VETERANS HEALTH ADMINISTRATION
OFFICE OF PATIENT CARE SERVICES
TECHNOLOGY ASSESSMENT PROGRAM

BRIEF OVERVIEW:

MANAGEMENT OF TOENAIL ONYCHOMYCOSIS

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TECHNOLOGY ASSESSMENT PROGRAM

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A SUMMARY FOR HTA REPORTS

VATAP is a member of the International Network of Agencies for Health Technology Assessment (INAHTA) [www.inahta.org]. INAHTA developed this checklist© as a quality assurance guide to foster consistency and transparency in the health technology assessment (HTA) process. VATAP added this checklist© to its reports in 2002.

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Brief Overview:
Management of Toenail Onychomycosis

September 2008

Item	Yes	Partly	No
Preliminary			
1. Appropriate contact details for further information?	√		
2. Authors identified?	√		
3. Statement regarding conflict of interest?			√
4. Statement on whether report externally reviewed?		√	
5. Short summary in non-technical language?			√
Why?			
6. Reference to the question that is addressed and context of the assessment?	√		
7. Scope of the assessment specified?	√		
8. Description of the health technology?	√		
How?			
9. Details on sources of information?	√		
10. Information on selection of material for assessment?	√		
11. Information on basis for interpretation of selected data?	√		
What?			
12. Results of assessment clearly presented?	√		
13. Interpretation of assessment results included?	√		
What Then?			
14. Findings of the assessment discussed?	√		
15. Medico-legal implications considered?			√
16. Conclusions from assessment clearly stated?	√		
17. Suggestions for further actions?	√		

ABBREVIATIONS

Bx/PAS biopsy with periodic acid-Schiff stain

CI, 95% confidence interval

CW, calcofluor white

CR, clinical response

DFN, disease free nail

DLSO, distal and lateral subungual onychomycosis

DM, German Mark (currency)

DTM, dermatophyte test medium

ELISA, enzyme-linked immunosorbent assay

EP, end point

FF, French Franc (currency)

FTO, full thickness onychodrystrophy

FU, follow up

GI, gastro-intestinal

GMS, Gomori methenamine silver

GP, general practitioner

IRON-CLAD, improving results in onychomycosis-concommitant Lamisil and debridement

ITT, intention to treat

KOH, potassium hydroxide

- **-DMSO** with dimethyl sulfoxide
- **-CBE** with chlorazol black

KONC, potassium hydroxide dissolution with centrifugation

- **-PA** (with PAS)
- **-FLU (**with fluorescent stain)
- **-BE** (with clorazol black E stain)

LION, Lamisil versus itraconazole in onychomycosis

MC mycologic cure

MRL, minimal residual lesions

N, number of patients (in study or group)

NNT, number needed to treat

NPV, negative predictive value

NS, not (statistically) significant

OD, optical density

PAS, periodic acid Schiff (staining)

PATHPAS, routine histo-pathological examination with PAS staining

PSO, proximal subungual onychomycosis

PPV, positive predictive value

RCT, randomized controlled trial

Se, sensitivity

Sp specificity

SWO, superficial white onychomycosis

TDO, total dystrophic onychomycosis

BRIEF OVERVIEW:

MANAGEMENT OF TOENAIL ONYCHOMYCOSIS

INTRODUCTION

"Onychomycosis is defined as a mycotic infection of the keratinized tissue of the nail plate and nail bed. The typical diagnosis is by a combination of clinical observation, fungal culture, and/or direct microscopy with potassium hydroxide (KOH). Occasionally, other methods such as periodic acid-Schiff or fluorescent staining techniques are used for enhanced sensitivity. The clinical features include subungual debris (severe thickened hyperkeratosis), discoloration, longitudinal darkened striations, thickening of the nail plate, onycholysis (detachment of the nail plate from the nail bed), and brittle damaged nail. Both topical and oral antifungal agents are used to effectively treat nail infections, with varying success." Tavakkol (2007).

*"**Trichophyton rubrum** is the most frequent causative agent of onychomycosis nail infection; it is isolated from 90% of nail samples that are culture positive….when terbinafine – the gold standard antimycotic drug therapy for toenail onychomycosis – is used, a mycologic cure rate of 66% to 89% can be achieved (negative KOH microscopy and negative culture). Reported infection relapse rates of 25% to 50% point to the need for a careful and sensitive method to substantiate the presence of cure after therapy because there is currently no method for determining whether relapse is due to failure to eradicate the initial infection or represents a new infection after successful therapy. Molecular biology methods may be more accurate for detecting subclinical infection than the traditional methods of light and calcofluor white microscopy and culture."* Gupta (2008).

Occasionally, this condition is also referred to as tinea unguium. Onychomycosis may be caused by dermatophytes, yeasts, and molds. A warm, moist environment favors mycotic infections…" Hettinger (1991).

*"Noninflammatory nail changes starting at the free edge of the nail are usually due to trauma, psoriasis, or a fungus infection. By contrast, the inflammatory processes are usually due to either bacterial or monilial (**Candida albicans**) infection and have their origin in the living tissue of the lateral walls of the nail groove."* Halprin (1968).

"In explaining nail disorders to the patient, the lowly fungus is frequently the scapegoat. Although fungi commonly infect nails, they are often falsely accused. One may avoid this error along with the misuse of costly therapy if it is recalled that the fungi infect the nail at its distal margin and then grow proximally in splinter-like projections, gradually destroying the ventral and then the dorsal part of the nail plate. Therefore, a nail dystrophy which appears first at the proximal nail fold cannot be due to fungus…" Madison (1965).

"Dermatophytes, yeasts, and molds can be the causative organisms of fungal nail infections. Alternatives to the systemic management of onychomycosis include topical and surgical treatments. Traditionally, topical agents used as monotherapy for onychomycosis are only able to inhibit the growth of fungal nail infections; clinical and mycologic cures have recently been observed after treatment with some of the newer preparations. In contrast, surgical treatments almost always need to be used in conjunction with ether topical or systemic antifungal therapy. An efficacious topical treatment alternative for onychomycosis involves applying antifungal agents concurrently or sequentially with removal or debridement of the infected nail structures…" Cohen (1994).

It is well known that in a large majority of cases in which onychomycosis is clinically evident, direct microscopy is negative. Even in those cases in which direct microscopy is positive, the culture can remain negative…" Heikkilä (1996).

"Both microscopy and culture performed on adequate specimens are essential for diagnostic accuracy…However, direct microscopy yields more than 10% false-negative data. In addition, discrepancies with culture occur in about one-third of cases, even with proper sampling and laboratory procedures. This in part due to the fact that fungi are modular organisms that can have visible but dead sections in direct microscopy. This leads to a KOH-positive, but culture-negative sample. Conversely, subungual scrapings samples may yield a few viable arthroconidia all but overlooked in direct microscopy although growing at culture. In these instances, the issue is a KOH-negative, but culture-positive sample." Arrese (2003).

"The current laboratory methods for diagnosing fungal infections of the nails are the potassium hydroxide (KOH) scraping technique and fungal culture. However, due to the long incubation period for fungal culture and the reported rate of approximately 30% false negative results observed when using these methods, a quick and highly specific screening test for onychomycosis is urgently needed." Reisberger (2003).

"Until recently, the only oral therapies available for the treatment of onychomycosis were griseofulvin and ketoconazole. These were relatively ineffective with poor response rates, long treatment times and a high relapse rate. Itraconazole, terbinafine and fluconazole have altered the way in which onychomycosis is treated, providing superior efficacy rates compared to griseofulvin and ketoconazole." Van Doorslaer (1996).

"There is wide variation in the methods of treating fungal infections of the skin and toe nails of the foot which reflects the uncertainty surrounding efficacy. Uncertainty also extends to the optimal period of treatment, appropriate dosage of drug, and frequency of application. Topical preparations are much less costly than orally administered antifungal drugs and cause minimal adverse side effects. However, whilst they may be helpful in treating symptoms in localized skin infections, uncertainty exists as to their efficacy in complete eradication of the infecting organisms. It has been suggested that fungal infected toe nails may be resistant to topical agents." Crawford (1999).

"…We consulted the local dermatology and podiatry departments and pharmaceutical advisor. The consensus was that treatment of toenail onychomycosis was necessary only if the infection was contributing to a biomechanical foot problem or if the patient also had neurological or circulatory problems. As a result we now explain to patients that they do not need treatment if the problem is purely cosmetic; most accept this. If treatment is indicated it is now started only after microbiological confirmation of infection. This policy has reduced our prescription rate to three courses of treatment over 12 months, compared with nine prescriptions over three months in 1996." Rose (1999).

"In recent years, much progress has been made in the oral treatment of onychomycoses. In fact, the pharmacokinetics and pharmacodynamics of triazoles and allylamines are such that the vast majority of onycomycoses should theoretically be cured in short treatment periods. However, this is not confirmed by clinical experience. To tackle better cure rates, doses of the antifungals were often increased or the duration of treatment modulated…." Piérard (2000).

"Functional faults of the foot may directly cause nail dystrophies, or may modify the presentation of pre-existing nail diseases. Any condition that alters the nail apparatus may have a significant effect on a person's ability to perform their normal activities of daily living. Multiple processes may be involved and common orthopaedic and podiatric considerations are often overlooked. We believe that fungal infection in the nails, particularly in the toes, is almost always a secondary phenomenon, often as a result of multiple causative factors. In addition to pre-existing pathology, all other possible contributory factors should be considered. These may include the aging population,

lifestyle factors such as sporting activities, occlusive footwear and communal bathing facilities, all of which may increase the risk of onychomycosis." Murray (2002)

"Dermatophyte fungi cause the overwhelming majority of toenail infections, and the available oral therapies are effective against all dermatophyte species. Therefore, in the majority of patients, diagnosis does not require identification of the genus or species of the pathogen, only determination of the presence or absence of dermatophytes. Laboratory fungal culture, together with KOH microscopy, is the traditional method for confirming a clinical diagnosis of toenail onychomycosis. As an alternative to lab culture, DTM culture is rapid, inexpensive, and easily performed in the primary care office..." Rich (2003).

"Antifungal treatments are often prescribed empirically, without mycological confirmation of the diagnosis. However, the ideal method for diagnosing onychomycosis remains unclear, as even in the best laboratories there is a false-negative culture rate in the order of 30%." Fletcher (2003).

"The traditional methods of dermatophyte morphotyping are hyphal microscopy of potassium hydroxide (KOH) wet-mount preparations (which identifies hyphae under low microscopic lighting), Calcofluor white stain, histologic staining using periodic acid (ρ-amino salicylic acid)-Schiff, and cultures. Although a KOH preparation, Calcofluor white stain or periodic acid-Schiff stain may be used to confirm the presence of fungi, a fungal culture is required to identify the specific genus and species of the infectious agent." Binstock (2007).

"Combination regimens are well-established for the treatment of several dermatological conditions, including psoriasis, acne vulgaris, rosacea, atopic dermatitis, and actinic keratosis. Combining 2 or more therapeutic approaches has the potential to increase cure rates, decrease intake of systemic antifungals, shorten treatment duration, and reduce drug acquisition costs, making the combination approach a logical consideration in the management of hard to treat moderate to severe onychomycosis. Ideally, a combination strategy should involve antifungal agents with complementary delivery systems, broad-spectrum activity, and complementary mechanisms of action." Gupta (2005).

"Successful treatment of onychomycosis in the infection site depends not only on achieving the minimal inhibitory concentration (MIC) of the antifungal agent, usually determined of fresh, proliferating fungal strains, but also on the effectivity against fungal spores dormant in nail keratin….This explains the high treatment failure and relapse rates observed under monotherapy of toenail onychomycosis even with modern antifungals Consequently, combined therapy is recommended, beginning with traumatic (chemical) removal of the affected toenails and continuing with an antifungal nail lacquer combined with a systemic antifungal." Seebacher (2003).

"The therapeutic outcome of onychomycoses is uncertain. Comparative short-term efficacy studies on antifungals abound and report contradictory findings. Few unbiased follow-up studies have scrutinized the long-term outcome. Basically, none of the current antifungals can guarantee cure in all instances. In addition, relapses are not rare. The causes of therapeutic failure in onychomycoses are multiple. The most important are the lack of diagnostic accuracy, inadequate antifungal choice or delivery, and presence of dormant conidia, sequestrated mycelium pockets or resistant fungal species. The concept of fungicidal drug derived from selected in vitro studies appears irrelevant in clinical practice." Arrese (2003).

"Several drugs have been approved by the US FDA for treatment of onychomycosis. The newer antifungal oral agents itraconazole and terbinafine are incorporated into the nail via both the nail matrix and the nail bed. The topical antifungal agent 8% ciclopirox nail lacquer, upon application, penetrates the nail plate to ultimately reach the nail bed. The time course required for visible clearance of the infection is dependant upon the rate of nail growth. As nail growth progresses from proximal to distal, which takes approximately

12-18 months, newly formed nail plate replaces diseased nail. Complete clearance occurs when the new nail is devoid of fungal infection. However, in some patients with severe onychomycosis, 5-10% of the nail surface will remain abnormal even when mycologic results indicate a full cure. Furthermore, treatment failures of up to 23-40% have been encountered, typically due to poor patient compliance, inadequate drug penetration, and fungal drug resistance.

Since efficacy parameters vary among clinical trials of toenail onychomycosis, a particular treatment cannot be judged solely on its trial failure/success rate. In order to evaluate the treatment outcomes of onychomycosis clinical trials, the clinician needs a clear understanding of trial efficacy parameters." Werchler (2004).

"The incomplete reproducibility of microscopic examination of KOH preparations for hyphae, and the even worse reproducibility of mycological culture, together with uncertain significance of both after drug therapy seriously limits their value…" Shuster (2001).

"Even with apparently optimal diagnosis and treatment, one in five onychomycosis patients are not cured by current therapies. The reasons for the 20% failure rate are inaccurate diagnosis, misidentification of the pathogen, presence of a second disorder, characteristics of the nails, presence of a high fungal inoculum and/or drug-resistant microorganisms, compromised immune system of the host, diabetes mellitus or peripheral vascular disease." Kaur (2008).

"Onychomycosis cure is defined by the absence of clinical signs or the presence of negative nail culture and/or microscopy results with one or more of the following minor clinical signs: (1) minimal distal subungual hyperkeratosis; and (2) nail-plate thickening. Clinical signs indicative of persistent onychomycosis at the end of the observation period include (1) white/yellow or orange/brown streaks or patches in or beneath the nail plate; and (2) lateral onycholysis with subungual debris. Although nail appearance will usually continue to improve after cessation of therapy, the nails may have a persistent abnormal appearance even in cases where treatment has been effective." Scher (2007).

"*Onychomycosis is as much a psychosocial issue as it is a medical issue. In addition to serving as a reservoir for fungal spread to other sites, onychomycosis can impact patients' quality of life. As many as 74% of onychomycosis patients report social embarrassment related to the disease. Anxiety, depression, loss of self esteem and confidence, avoidance of intimacy, and impaired relationships are among the negative impacts reported. Without treatment toenails can become thick, causing pressure, irritation, and pain…Dystrophic toenails may predispose to secondary bacterial infections. Therefore, treatment may be indicated from both medical and psychosocial perspectives."* Finch (2007).

"Onychomycosis affects up to 10% of the general population and is associated with functional impairment. Clinically, onychomycosis can mimic nail psoriasis, trauma, lichen planus, onychogryphosis, and other disorders. Laboratory methods for diagnosing onychomycosis vary in accuracy and predictive value. Clinical cues to onychomycosis would help to guide laboratory testing and decrease improper empiric antifungal therapy." Walling (2007).

Despite renewed interest in the pharmaceutical treatment of onychomycosis, it is often still necessary to treat certain infections in a surgical manner. Such cases include the severely thickened, very painful or severely dystrophic mycotic nail. In some cases, surgical treatment may be combined with pharmaceutical therapy…" McInnes (1997).

"Onychomycois is the most common nail disease encountered by dermatologists. The history of the treatment of fungal infections is long but the history of development of pharmacological drugs to combat fungal infections of the nail is much more recent. Fungi are eukaryotic organisms and eradication of the offending pathogen has been costly, lengthy, and of great risk to the patient, without necessarily being truly effective. In more recent times, development of new drugs and treatment modalities has led to the assumption that, with the therapeutic arsenal at our disposal, these infections will

become things of the past. However, it has become clear that a substantial proportion of patients do not enjoy a complete and lasting cure. Onychomycosis may not, in most cases, be life-threatening, but it is a life-impairing disease: several studies have documented the effects on patient quality-of-life…problems of methodological consistency. These include the lack of a universally accepted severity scoring scale for nail disease, the institution of clearly defined end points and efficacy criteria, in addition to a disease severity classification, all of which are required in this field. The lack of such guidelines would not be tolerated in many therapeutic areas." Baran (2001).

BACKGROUND

VHA's Podiatry Service asked the VA Technology Assessment Program (TAP) to review published literature on fungal toenail infection as support for a national information letter regarding management of these common conditions. The excerpts quoted above indicate the evolution of treatment approaches over the past decades as well as continuing uncertainty regarding optimal management.

Podiatry's initial request was followed by a series of more specific clinical questions still focusing on onychomycosis, and then by a third request for review of basic foot care or primary foot care research. For onychomycosis, the Service specifically excluded non-dermatophyte infections from TAP consideration.

In other words, TAP's charge from Podiatry covered two relatively distinct bodies of literature: dermatophyte onychomycosis and primary foot care. This overview thus has a companion document, "Foot Care Interventions". Although each is intended to be free-standing, together they constitute TAP's response to Podiatry Service.

METHODS

In context of its broad initial charge for onycomycosis, TAP first identified available systematic reviews. Such reviews, defined below, provide a rigorous and immediately accessible "snapshot" of the extent to which research has progressed toward definitive testing of alternate therapies' effectiveness or cost-effectiveness, while highlighting gaps in the knowledge base to guide question refinement for further literature synthesis.

Selection criteria

Reviews and primary research were further required to be full-text available in English, to involve adult human subjects, and to have been published or updated since 1990. Final updated searches were conducted on July 21, 2008. For selected questions, such as relative accuracy of diagnostic tests (Appendix Table 3), we ran additional searches without date or language restrictions, in efforts to identify any critical research published within the time period covered by electronic database indexing.

The quotations on pages one through five were selected not because their source articles represent compelling evidence, but because they cogently capture areas of ongoing discussion or uncertainty relevant to this review. Only those articles referenced and abstracted in the tables should be considered as meeting inclusion criteria and thus contributing substantively to the issues under discussion here.

TAP excluded:

- Pre-clinical or laboratory research;
- Articles with insufficiently clear methods reporting to determine study design or critical details such as the gold standard for diagnostic accuracy comparisons;

- Single case reports;
- Analyses restricted to fingernails or those in which finger-and toe-nail data were not separately reported;
- Purely descriptive case series or pilot studies;
- Narrative reviews, opinion pieces, and other publications lacking either primary clinical data or explicit methods reporting;
- Primary studies already included in systematic reviews.

Systematic reviews

Cook (1997) and Mulrow (1997) state: *"Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews, which synthesize a selection of articles without defining a research question, or reporting methods of selection or quality criteria, and thus are prone to significant bias.

Systematic reviews:

- Ask a focused clinical question.
- Conduct a comprehensive search for relevant studies using an explicit search strategy.
- Uniformly apply criteria for inclusion and exclusion of studies.
- Rigorously and critically appraise included studies.
- Provide detailed analyses of the strengths and limitations of included studies.

Systematic reviews can be quantitative (i.e., meta-analytic, applying statistical methods to the summary of study results) or qualitative; in either case the inferences or conclusions of the review must follow logically from the evidence presented.

The rigor of this approach is illustrated by the place of systematic reviews in evidence grading schemes (Cook, 1995; Guyatt 1995), where they receive the highest level designation. This overview includes any review meeting the definition of systematic, whether meta-analytic or qualitative. We cite Cochrane Collaboration protocols (reviews in the planning stage), as they provide advance notice of issues likely to be resolved by systematic reviews in the near future.

Search strategy

TAP searched Medline and the Cochrane library using the terms " toenail", "onychomycosis", "review", and "meta-analysis" for the years 1990 to 2008 to identify systematic reviews published in English and covering research using adult human subjects. Since economic evaluations often use efficacy data from systematic reviews, we also retrieved economic evaluations identified by these searches.

Additional questions

In a second stage of activity, Podiatry Service clinicians framed additional research questions, also focused on onychomycosis. Search methods for both parts of TAP activity were essentially the same, although TAP identified primary research along with reviews for the added questions. Research questions and responding literature for the second stage are provided in Table 3 (Appendix). For Table 3, we excluded primary research studies published in years and/or covering topics already included in one or more systematic reviews. Exclusion criteria were otherwise identical to those detailed above.

One reviewer (KF) selected materials, abstracted included studies, and prepared this brief overview.

RESULTS

Comprehensive search strategies and rigorous exclusion criteria produced an impressive number of citations (reference list pages 45 to 50) but in fact a relatively slender body of research literature providing credible responses to Podiatry's multiple research questions as discussed below. Reviews from the Cochrane Collaboration (www.cochrane.org) set the standard for methodological rigor and validity of results, hence are identified as such in all tables.

Table 1 overviews availability of systematic reviews, while Table 2 summarizes results. The appendix tables provide greater detail for individual reviews.

Table 1 confirms that systematic review coverage is currently limited to topical and systemic antifungal agents; others among the clinical questions in Appendix Table 4 have yet to be addressed by systematic reviews. Table 4 provides brief summaries of the state of research knowledge for individual clinical questions.

Table 1. Availability of systematic reviews and economic evaluations: fungal infections of the toenails (English, 1990-2008)

Notes:

- **Light shaded rows indicate research conducted with pharmaceutical company funding or declaration of interest by an author.**
- *** indicates a review indexed or titled as systematic, which on close inspection does not fully qualify**

Citation	Intervention(s) covered
Reviews from the Cochrane Collaboration	
Bell-Syer (2004): protocol	Oral treatments for toenail onychomycosis
Crawford (1999; 2007)	Duplicates Hart (1999) below
Two Cochrane reviews; one protocol	**One for skin and nail infections; one for skin only; toenail pending**
Other systematic reviews, guidelines, or assessments	
Cribier (2004)	Terbinafine in high-risk populations (immunocompromised, diabetes, HIV) and non-dermatophyte infections.
Gupta (2004)	Cumulative meta-analysis; Oral anti-mycotic agents: • terbinafine; • itraconazole (pulse or continuous); • Flucnazole; • Griseofulvin.
Casciano (2003)	Oral and topical therapies for toe and fingernail infections: • Continuous itraconazole; • Pulse itraconazole; • Cioclopirox.
Krob (2003)	Terbinafine Vs itraconazole.
Roberts (2003)*	British Association of Dermatologists guideline covering epidemiology, diagnosis, and treatment.
Crawford (2002)	Oral treatments: Continuous terbinafine Vs. continuous itraconazole (2 trials).
Gupta (2003)	Efficacy criteria used in trials of systemic treatments for dermatophyte infections: • Grieofulvin; • Ketonaconazole; • Terbinafine (continuous and pulse);

Citation	Intervention(s) covered
	• Itraconazole (continuous and pulse); • Fluconazole
Haugh (2002)	Terbinafine Vs: • Placebo (3 trials); • Itraconazole (4 trials); • Griseofulvin (2 trials).
Cribier (2001)	Long-term efficacy of antifungal agents
Gupta (2000)	Economic analysis: ciclopirox nail lacquer 8% Vs: • Terbinafine; • pulse and continuous itraconazole; • fluconazole; • griseofulvin; • US$ in 2000.
Hart (1999)	Topical treatments for nails (2 trials): • 2 amorolfine 5% nail lacquer formulations with different vehicles; • Clotrimazole solution Vs tea tree oil.
Epstein (1998)	Disease-free nail rate from oral treatment
Other systematic reviews:16	**Oral and topical agents, general and specific (high-risk) populations, qualitative and quantitative reviews**
Economic analyses	
Gupta (2002)	Antimycotic agents: • Ciclopirox 8% nail lacquer; • Terbinafine; • Pulse and continuous itraconazole; • Fluconazole; • Griseofulvin; • USA 2001 from perspective of third-party payer.
Jansen (2001)	Cost-effectiveness (from LION study: continuous terbinafine Vs intermittent itraconazole)
Gupta (1999)*	Oral antifungal agents (itraconazole, terbinafine, fluconazole):Vs griseofulvin
Mehregan (1999)*	Testing Vs empiric treatment
Bootman (1998)	Terbinafine Vs Itraconazole
Van Doorslaer (1996)	Germany: • Itraconazole continuous and 1-week pulse; • Oral terbinafine; • Ciclopirox nail varnish.
Arikian (1994)	Economic evaluation: oral therapies for onychomycosis in Austria, Belgium, Canada, Finland, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Switzerland, UK.
Einarson (1994)	Cost-effectiveness (Canada; government payer): oral antifungal agents: • Griseofulvin; • Ketoconazole; • Terbinafine
Economic analyses: 8	**Systemic and topical agents, various regimens, countries, perspectives; some articles represent cost studies without consideration of outcomes, hence are not full economic evaluations.**

SUMMARY AND DISCUSSION

The only certainties offered by the literature covered for this review are captured in systematic reviews (Table 1 above; overviewed results in Table 2 below, full details in Appendix Table 3, and some duplication for ease of reading in Appendix Table 4). The research responding to certain of the clinical questions in Table 4 (specifically comparative diagnostic test accuracy; management of onychodystrophy to the extent that it is distinct from dermatophyte infection; and control versus cure) is non-existent or virtually so, of low quality or impenetrably reported, and generally inadequate to provide definitive answers.

A cursory scan of study types in the literature can be deceiving: while RCTs of some treatments (Tables 1-4) have been published, many trials fail to meet methods quality standards such as reporting of sample size calculations and randomization methods (Guyatt, 1993; Mulrow, 1996). Formal economic evaluations require analyses of both costs and consequences of alternate technology use (O'Brien, 1997). However, the publications titled or indexed as economic evaluations for this review (Tables 1 and 2) often fail to explicitly report: perspectives; full details on costs and assumptions; evidence for outcomes; and sensitivity analyses.

CONCLUSIONS

More rigorous research, well-designed, clearly reported, and carefully edited, is needed to fully support evidence-based guidance for management of toenail onychomycosis. Finally, there is a clear need for systematic reviews dedicated to individual specific clinical questions, along with the standardization of disease severity and outcome measures that would facilitate such reviews.

> *"We need less research, better research, and research done for the right reasons."*
> Altman (1994).

Table 2 summarizes results of systematic reviews and economic evaluations of treatments for which such reviews are available.

Table 2. Treatment of toenail onychomycosis: summarized results of systematic reviews and economic evaluations for topical and systemic antifungal agents

Notes:
- **full details for individual reviews in Appendix Table 3**
- **light-shaded cells indicate concurrence of review findings**
- **reviews with objectives other than drug-to-drug or -placebo comparisons not included**
- **where multiple publications cover the same content, only the most recent is included**
- **Cochrane protocols not included.**

Review	Findings/comments
Topical agents	
Crawford (2007)	**Cochrane review**: 6 trials of topical agents • Evidence for topical treatments is sparce. • Some evidence that clopiroxolamine and butenafine are effective but need daily application for prolonged periods. • Amorolofine may be more effective but more research is needed.
Gupta (2002)	Ciclopirox 8% lacquer is cost-effective.
Gupta (2000)	Ciclopirox 8% lacquer is cost-effective compared with oral regimens
Hart (1999)	2 trials of topical agents for nail infections: • neither showed significant difference between agents; • Most cost-effective strategy: first treat with azoles or undecenoic acid, use allylamines only if first treatment fails.
Systemic agents	
Krob (2003)	Terbinafine was generally superior to itraconazole although either was superior to placebo.
Casciano (2003)	40 trials with 3248 patients: • Terbinafine success, 81.15%; relapse, 6.42%; • Terbinafine is the most cost-effective agent; • Increased utilization of terbinafine would reduce managed care per member per month costs.
Crawford (2002)	Meta-analysis of two trials: terbinafine Vs continuous itraconazole: • Significantly in favor of terbinafine at 11 and 12 months, risk difference -0.23 (CI, -.32—0.15); • NNT, 5 (CI, 4-8). • Continuous terbinafine is the most effective oral regimen. • Most trials funded by pharmaceutical industry.
Jansen (2001)	Cost-effectiveness based on LION study data: • Cure rate of terbinafine for 12 weeks, 76%; 16 weeks, 81%; • Cure rate for itraconazole pulse, 38-49%; • Terbinafine significantly better at 72 weeks and most cost-effective for health care system.
Gupta (2000)	Cost/cure (US$ in 2000): • Ciclopirox, 618.2; • Itraconazole pulse, 1146.4 • Terbinafine, 1153; • Fluconazole, 1473.7; • Itraconazole continuous, 2126.9; • Griseofulvin, 3438.2 Relative cost-effectiveness: • Ciclopirox, 1.00; • Pulse itraconazole, 1.19; • Fluconazole, 1.24; • Terbinafine, 1.27; • Continuous itraconazole, 2.08; • Griseofulvin. 3.13
Gupta (1999)	Cost-effectiveness (US, '98/'99):

	• Most cost effective agents: pulse itraconazole and terbinafine; • Least cost-effective: griseofulvin.
Epstein (1998)	Effectiveness in achieving disease free nail: • Terbinafine, 30-35% (CI, 38-55%); • Itraconazole, 25-40% (CI, 25-45%); • One-year failure rate, 45%
Van Doorslaer (1996)	Economic analysis for Germany: • Clinical cure at end of follow up: itraconazole pulse, 72.5%; terbinafine, 72.5%; itraconazole continuous, 49.3%; • Itraconazole pulse had the most favorable cost-effectveness ratio; • Sensitivity analysis: relative ranks of agents changed when efficacies changed, so overall results not conclusively in favor of either drug.
Einarson (1994)	Cost-effectiveness in Canada: • Success rates: terbinafine, 78%; ketonazole, 41%; griseofulvin, 18%; • Same order for disease free days • Cost effectiveness ratios: terbinafine, 1; griseofulvin, 2.5; ketonazole, 2.5; • Terbinafine is the most cost-effective agent
Arikian (1994)	Cost effectiveness in western Europe and Canada: Terbinafine had highest success rate and was most cost-effective of comparators.
Overall results	With few exceptions, Terbinafine remained the most effective and cost-effective treatment in reviews published 1994-2003. Pulse itraconazole had equivalent cost-effectiveness among oral agents in some studies, depending on perspective and currency. No single topical agent was identified as most effective or cost-effective and too few studies directly compared topical and oral agents to generalize from results. All antifungal agents have substantial relapse or reinfection rates.

APPENDIX

Table 3: Abstracted details of systematic reviews, economic evaluations, technology assessments, guidelines or policy statements)

Notes:
- **Lighter-shaded rows indicate studies conducted with pharmaceutical company funding or declaration of interest by an author.**
- **(*) indicates review indexed or titled as systematic but which on close inspection does not fully qualify;**
- **See Table 2 for summarized results of reviews.**

Citation	Objective	Included studies	Results/Conclusions
Reviews from the Cochrane Collaboration			
Bell-Syer (2004)	To assess the effects of all oral treatments for toenail onychomycosis		Protocol: review in planning stage
Crawford (1999; 2007) Original review and update	To assess effects of topical treatments in successfully treating (rate of failure) fungal infections of the toenails and in preventing recurrence	• RCTs enrolling patients with culture-diagnosed fungal infections of toenails; • Multiple databases, inception - 2005.	**Placebo comparison:** • Ciclopiroxolamine Vs placebo: RR, 0.32; CI, 0.20-0.52 at 48 weeks; • Fungoid tincture Vs placebo: RR, 0.17; CI, 0.02-1.14 at 12 months; **Treatment Vs treatment:** • 2% butenafine Vs 5% tea tree oil: RR, 0.03; CI, 0.00-0.47 at 36 weeks; • 1% clotrimazole Vs tea tree oil: clotrimazole better but NS; • Two 5% amorolfine lacquer formulations with different vehicles used twice weekly for 4 weeks both achieved RR of 1.00; CI, 0.85-1.18 at 3 and 14 days after end of treatment; **Conclusions*: "****Evidence for the management of topical treatments for infections of the toenails is sparse. There is some evidence that ciclopiroxolamine and butenafine are both effective but they both need to be applied daily for prolonged periods (at least one year). The six trials of nail infections provided evidence that topical ciclopirololamine has poor cure rates and that amorolofine might be substantially more effective but more research is required."*
Other systematic reviews, assessments, guidelines			
Cribier (2004)	To review published studies of the safety and efficacy of terbinafine in special patient populations: • Diabetes mellitus; • HIV infection; • Receiving immunosuppressive therapy;	• Medline to October 2002; • Meeting abstracts; • No study design requirements	**Diabetes:** • 3 studies (total n = 217); designs not reported • Mycological cure rates at the end of FU: 64%-89%; • Cure rates in ITT analyses (2 studies from which review authors could calculate): 62%; 78%; • ITT complete cure rate: 41%; • No significant side effects; • Tolerability "very good" in 91% of patients;

Citation	Objective	Included studies	Results/Conclusions
	• Onychomycosis due to non-dermatophyte infection.		• NS differences in mycological or clinical cure rates for diabetics Vs non-diabetics; **HIV:** • 2 studies (total n = 31); designs not reported; • Mycological cure in 30%. **Organ transplant recipients:** • 3 case series (total N = 45); • Cure rates, 86-100%; • Significant decrease in blood cyclosporin levels with terbinafine, but not reflected in clinical status. **Non- dermatophyte infection:** • 11 clinical trials or case series; • Total N = 389; • Wide range of pathogens and methods of recording outcome; • This review does not pool results. **Conclusions:** *This review suggests that terbinafine is a safe and effective treatment for onychomycosis in high risk populations. However, the majority of these studies only included small numbers of patients and larger clinical trials are needed, especially in patients with HIV infection."*
Gupta (2004)	A cumulative meta-analysis to determine: • Whether the cure rate for systemic antifungal agents has remained consistent over time; • Mycological and clinical response rates in open Vs randomized studies	• Studies evaluating efficacy of oral antifungal agents (terbinafine; pulse or continuous itraconazole; fluconazole; griseofulvin); • Standard accepted dosage regimens, treatment duration, and FU; • Medline 1966-2002	36 studies included: • RTCs: change in efficacy, first trial to overall cumulative meta-average: terbinafine, 78%±6% to 76 ± 3% (P = 0.68); itraconazole pulse, 75 ±10% (P =0.25); itraconazle continuous,63 ±5% (P = 0.47); fluconazole, 53 ±6% (P = 0.41); griseofulvin, 55± 8% P = 0.41); • RCTs Vs open studies, mycological cure rates: terbinafine, 76 ±3% Vs.83 ± 2% (P = 0.0028); itraconazole pulse, 63±7% Vs. 84± 9% (P = 0.0001); fluconazole, 48 ± 5% Vs. 79 ± 3% (P = 0.0001). **Conclusions:** *"The cumulative meta-analysis of cure rates for RCTs suggests that over time, as new RCTs have been conducted, the efficacy rates have remained consistent. The efficacy rates of open studies are substantially higher compared to RCTs and may therefore over estimate cure rates."*
Krob (2003)	To compare the efficacy of terbinafine with that of itraconazole in the treatment of dermatophyte toenail onychomycosis	• Placebo-controlled trials or terbinafine-itraconazole comparisons whose patients received at least 3 but not more than 4 months or cycles of either	9 trials in meta-analysis: • Terbinafine Vs. itraconazole (6 trials): terbinafine was superior to itraconazole, pooled OR, 2.85(CI, 1.96-4.13); pooled OR by another method, 1.77 (CI, 1.11-2.83); • Terbinafine Vs. placebo (1 trial): OR, 44.9 (CI, 7.2-281); or 48.7 (8.5-280);

Citation	Objective	Included studies	Results/Conclusions
		drug; • Diagnosis confirmed by culture; • Outcome assessed by culture; • Count of patients enrolled for ITT; • Count of evaluable patients; • Doses limited to 250mg/day terbinafine or monthly pulse of500mg/day for 1 week; 200 mg/day itraconazole or monthly pulse of 400mg/day for 1 week; • English, 1966-June 1999; • Excluded: subjects received active treatment during FU; trials with < 20 subjects; studies without pre-established treatment duration; studies evaluating only treatment group by culture.	• Itraconazole Vs placebo (2 trials): pooled OR, 25.5(10.3-62.8); or 29.2(12.6-67.8). **Conclusions:** *"Meta-analysis of the published worldwide literature finds that terbinafine is significantly more effective than itraconazole at achieving mycologic cure of toenail onychomycosis* **."**
Roberts (2003)*	To present evidence-based guidance for treatment with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.	Not reported	**Distal and lateral subungual onychomycosis:** DLSO accounts for the majority of cases and is almost always due to dermatophyte infection. **Superficial white onychomycosis:** SWO is nearly always due to a dermatophyte infection, most commonly *T. mentagrophytes.* **Proximal subungual onychomycosis:** PSO without evidence of paronychia is an uncommon variety of dermatophyte infection often related to intercurrent disease (immunosuppression or HIV+). **Total dystrophic onychomycosis:** Any of the above varieties of onychomycoses may eventually progress to total nail dystrophy, where the nail plate is almost completely destroyed. **Conclusions:** • *"Treatment should not be commenced before mycological confirmation of infection.* • *Dermatophytes are by far the commonest causal organisms.* • *Culture of yeasts and nondermatophyte moulds should be interpreted carefully in each individual case. In the majority, yeasts are likely to be a secondary infection and nondermatophyte moulds to be saprophytic in previously damaged nails.* • *Topical treatment is inferior to systemic therapy in all but a small number of cases of very distal infection or in SWO.* • *Terbinafine is superior to itraconazole both in vitro and in vivo for dermatophyte onychomycosis, and should be considered for first-line treatment, with*

Citation	Objective	Included studies	Results/Conclusions
			itraconazole as the next best alternative. • *Cure rates of 80-90% for fingernail infection and 70-80% for toenail infection can be expected. In cases of treatment failure the reasons for such failure should be carefully considered. In such cases either an alternative drug or nail removal in combination with a further course of therapy to cover the period of regrowth should be considered.""* **Audit points:** • Has a positive culture been obtained before commencing systemic therapy for onychomycosis? • Has an appropriate agent been chosen, based on the type of organism cultured? • Are arrangements in place for adequate duration of treatment to be supplied from hospital or general practitioner? • Has immunosuppression been considered in cases of PSO?
Crawford (2002)	To identify and synthesize the evidence for the efficacy of oral treatments for fungal infections of the toenails.	• RCTs; • Microscopy and culture to confirm presence of dermatophytes; • Excluded: trials also evaluating fungal infections of fingernails in which foot-specific data were not included; trials including patients with yeast or mold infections.	Pooled analysis of two trials comparing mycological cure rates: terbinafine (250mg/day for 12 weeks) Vs. continuous itraconazole (200mg/day for 12 weeks): • Statistically significant difference in favor of terbinafine for 11- and 12-month outcomes; • Risk difference, -0.23 (CI, -.32 to -0.15); • NNT, 5 (CI, 4-8); • Analysis of clinical cure rates was not possible due to variety of definitions used in effectiveness studies. **Conclusions:** *"There is good evidence that a continuous regimen of terbinafine (250mg/d) for 3 months is the most effective oral treatment for fungally infected toenails. Consensus among researchers evaluating oral antifungal drugs for onycomycosis is needed to establish meaningful definitions of clinical cure. Most trials were funded by the pharmaceutical industry; we found little independent research, and this may have introduced bias to the review."*
Crawford (1999); duplicates Hart (1999)	To summarize evidence for topical antifungals in toenail infections.	Medline, Embase, Cochrane controlled trials register: • To May 2000 and subsequent RCTs; • All languages; • Excluded: foot-specific data could not be extracted; studies that did not use culture for diagnosis and as outcome measure	• RCTs with no language restrictions; • topical treatments; • fungal infections of skin and nails of feet; • Skin infection trials needed culture and microscopy to establish presence of dermatophytes; • Nail infection trials needed culture to establish presence of dermatophytes; • Excluded: trial covering sites other than foot where data specific to foot could not be extracted.
Gupta (2002)	To determine the cost-effectiveness of therapies for	MEDLINE/EMBASE: • Articles in English;	Costs per patient, per mycologic cure, and per disease free day tabulated in the article.

Citation	Objective	Included studies	Results/Conclusions
	dermatophyte toenail onychomycosis in the United States in 2001.	• 1966-2000; • Excluded: reviews; • Treatment algorithm developed; • Meta-analysis to calculate average mycologic and clinical response rates for various agents (ciclopirox nail lacquer 8%; pulse and continuous itraconazole, griseofulvin, fluconazole, terbinafine).	**Conclusions:** ***"…****ciclopirox 8% nail lacquer, which has recently become available in the larger size of 6.6mL, is a cost-effective agent for the management of toenail onychomycosis."* .
Cribier (2001)	To analyze therapeutic results recorded > 1 year after initiation of therapy	MEDLINE to June 2000: • Studies reporting results> 1 year after initiation of therapy with amorolofilne, ciclopiroxolamine, fluconazole, griseofulvine, itraconazole, ketoconazole, or terbinafine; • Results of mycologic examination (direct and culture); • Endpoints: EP-1, number of patients with negative culture after FU/number of patients at day zero; EP-2, number of patients with negative culture after FU/ patients with negative culture at week 48; EP-clinical, number of patients cured (total recovery or > 90% improvement at >1 year; • Included study designs not otherwise defined.	17 studies reporting results> 48 weeks: • Ketoconazole 200mg/day: EP-1, 11% at 18 months; EP-2, 43%; • Griseofulvin, 1g/day: EP-1, 43% at 18 months; EP-2. 72%; • Fluconazole once/week up to one year: EP-1, 49% at 18 months; EP-2, 91%; • Itraconazole 200mg/day or 400 mg/day 1 week each month for 3-4 months: EP-1, 37% at18 month, 53% at 2 yrs; EP -2, 76% at 4 years; • Terbinafine 250 mg/day for 12-16 weeks: EP-1, 62% at 18 months, 72% at 2 yrs, 60% at 4 yrs; EP-2, 80% at 18 months, 81% at 2 yrs, 71% at 4 yrs; • In the only study comparing long-term efficacy of terbinafine Vs itraconazole, EP-1 at 18 months was significantly higher (66% Vs 37%, p<0.001) with continuous terbinafine that intermittent itraconazole; • Clinical cure rates: 21% at 60 weeks and 37% at 72 weeks with fluconazole; 27% at 18 months, 35% at 2 yrs with itraconazole; 48% at 18 months, 69% at 2 yrs, 50% at 4 yrs with terbinafine; **Conclusions:"***…this critical review suggests that the long-term efficacy achieved with terbinafine is superior to that obtained with griseofulvin, ketoconazole, fluconazole, or itraconazole."*
Gupta (2000)	To determine the most cost-effective treatment for dermatophyte onychmycosis of the toes in the United States in 2000.	English language: • 1966-1999; • Discussion of efficacy of comparators (griseofulvin, terbinafine, pulse or continuous itraconazole, fluconazole, ciclopirox nail lacquer). • Clinical and mycologic diagnosis of onycomycosis with distinction dermatophye Vs. non-	**Outcome rates by drug:** • Ciclopirox: MC, 52.6±4.2%; CR, 52.4±9.0%; • Griseofulvin: MC, 41.1±20.4%; CR, 33.7±14.1%; • Continuous itraconazole: MC, 66.3±4.2%; CR, 70.3±4.2%; • Pulse itraconazole: MC, 70.8±5.7%; CR, 73.6±4.6%; • Terbinafine: MC, 77.2±4.0%; CR, 75.3±2.9%; • Fluconazole: MC, 65.6±7.1%; CR, 66.5±11.7%; **Cost per regimen (US$):** • Ciclopirox, 325.2;

Citation	Objective	Included studies	Results/Conclusions
		dermatophyte • Required duration of study: griseofulvin (>6 months); itraconazole (≥ 3 months); terbinafine (≥ 3 months); fluconazole (≥ 3 months; ciclopirox (≥ 6 months). • Required dosage: griseofulvin (500mg/day); itraconazole pulse (200mg bid for 1 week each month and successive pulses 1 month apart); itraconazole continuous (200 mg/day; terbinafine (250mg/day); fluconazole (q7d); ciclopirox applied once weekly to daily); • End-point of therapy clearly defined; • Site of infection clearly defined.	• Griseofulvin, 1413.1; • Continuous itraconazole, 1410.2; • Pulse itraconazole, 811.7; • Terbinafine, 890.1; • Fluconazole, 1473.1; **Cost/cure and/symptom free day:** • Ciclopirox, 618.2, 1.69; • Griseofulvin, 3438.2, 5.3; • Continuous itraconazole, 2126,9, 3.52; • Pulse itraconazole, 1146.4, 2.01; • Terbinafine, 1153.0, 2.04; • Fluconazole, 1473.7, 2.10; **Relative cost-effectiveness :** • Ciclopirox, 1.00; • Pulse itraconazole, 1.19; • Fluconazole, 1.24; • Terbinafine;, 1.27; • Continuous itraconazole, 2.08; • Griseofulvin, 3.13. • Sensitivity analyses indicated that ciclopirox was cost-effective compared with oral regimens. **Conclusions:** *"Ciclopirox nail lacquer 8% is a recent addition to the armamentarium of therapies available to the physician and patient for the treatment of onychomycosis. The nail lacquer is a cost-effective agent compared with the oral antifungal therapies, terbinafine, itraconazole, fluconazole, and griseofulvin."*
Hart (1999)	To identify and synthesize the evidence for efficacy and cost effectiveness of topical treatments for superficial fungal infections of the skin and nails of the feet.	• RCTs with no language restrictions; • topical treatments; • fungal infections of skin and nails of feet; • Skin infection trials needed culture and microscopy to establish presence of dermatophytes; • Nail infection trials needed culture to establish presence of dermatophytes; • Excluded: trials covering sites other than foot where data specific	126 trials in 121 papers identified: • 72 (57.1%) met inclusion criteria; 2 trials for nail infections; • Neither trial of nail infections showed significant differences between alternative topical treatments. **Conclusions:** *Allylamines, azoles, and undecenoic acid were efficacious in placebo-controlled trials. There are sufficient comparative trials to judge relative efficacy between allylamines and azoles. Allylamines cure slightly more infections than azoles but are much more expensive than azoles. The most cost effective strategy is first to treat with azoles or undecenoic acid and to use allylamines only if that fails."*

Citation	Objective	Included studies	Results/Conclusions
		to foot could not be extracted.	
Gupta (1999)	To determine the most cost-effective treatment for dermatophyte onychomycosis of the toenails in the USA in 1998/1999.	• English language studies using itraconazole, terbinafine, fluconazole, or griseofulvin to treat onychomycosis of the toenails; • 1966-1999; • Preference for RCTs, but other types were included.	Article tabulates efficacy and cost results but does not summarize in text. • The two most cost-effective agents for dermatophyte onycomycosis are pulse itraconazle and terbinafine, followed by fluconazole, continuous itraconazole, and griseofulvin; • Sensitivity analysis with minor changes in efficacy rates reverses the rank order of pulse itraconazole and terbinafine. **Conclusions:** *"The two most cost-effective regimens for the treatment of dermatophyte toenal onychomycosis are itraconazole (pulse) and terbinafine; the least cost-effective comparator is griseofulvin, despite the fact that it has the cheapest drug acquisition cost per tablet."*
Epstein (1998)	To analyze studies on oral treatment of toenail onycomycosis to aid clinical decisions	Medline: • Description of results in toenails; • Culture and microscopy plus clinical evaluation; • Excluded: single case reports; series< 15; results combining finger- and toenails; report of toe nails cured but not subjects.	26 articles: • Standard course of terbinafine: DFN in 35-50% (CI, 38-55) of patients; itraconazole, 25-40% (CI, 25-45); • 45% of patients showed mycological failure during one year. **Conclusions:** *"Standard courses of terbinafine achieved a disease free nail in approximately 35% to 50% of patients. For itraconazole, the relevant disease-free nail rate was about 25% to 40%. Disease reappearance is an important issue; unfortunately data are lacking as to its frequency."*
Economic evaluations			
Casciano (2003)	To evaluate from a managed care organization perspective the relative cost-effectiveness of different treatment options.	• Medline and Embase; • 1985-2001; • Adult patients with dermatophyte infections; • Success defined as mycological cure; • Dosage and treatment length within suggested ranges; •	40 clinical trials with 3248 patients: • Terbinafine has the highest success rate for both fingernails (96.55%) and toenails (81.15%); • Terbinafine also had the lowest relapse rate: 6.42%; • Terbinfine dominated all comparators for cost-effectiveness (fingernails and toenails); **Conclusions:** *"Based on the patient-level analysis, we concluded that terbinafine is the most cost-effective therapy in the management of onychomycosis from a managed care perspective. Furthermore, at the policy level, increased utilization of terbinafine among onychomycosis patients is likely to reduce the managed care organizations' per member per month cost."*
Jansen (2001)	To compare costs and effectiveness of two treatment regimens for dermatophyte onychomycosis: • Continuous terbinafine; • Intermittent itraconazole.	**Cost-effectiveness analysis using data from LION study: double-blind multicenter RCT** • Adults (18-75) with dermatophyte nychomycosis; • Excluded: use of drugs known or	**496 (or 506) patients randomized:** • T12 group, 126 patients; • T16 group, 123; • I3, 131 (CI, 41-107); • I4, 126. Mycological cure rates: T12, 76%; T16, 81%; I3, 38%; I4, 49%;

Citation	Objective	Included studies	Results/Conclusions
	Randomization to 4 parallel groups: • Terbinafine 250mg/day for 12 or 16 weeks (groups T12 and T16); • Itraconazole 400 mg/day for 1 week in every 4 weeks for 12 or 16 weeks (groups I3 and I4); Perspective: health care system (Finland, Germany, Iceland, Italy, Netherlands, UK).	believed to interact with either study agent • Costs (direct medical costs only) estimated from expert opinion to the study sample	Complete cure (mycological cure plus 100% toenail clearing) rates: T12, 45.8% (CI, 6.4-55.3); T16, 55.1% (CI, 45.0-65.0); I3, 23.4% (CI, 15.4-31.3); I4, 25.9% (CI, 17.70-34.0). Percentage of patients completely cured at week 72 in terbinafine groups (T12, T16) was significantly greater ($P \leq 0.0046$) than those initraconazole groups. **Conclusions:** *"From the perspective of the healthcare system, continuous terbinafine is less costly and more effective than intermittent itraconazole."*
Mehregan (1999)*	Economic evaluation: testing Vs empiric treatment **Case series:** • **cost study only;** • **outcomes not considered.**	Not reported	688 dystrophic nail samples from the same number of patients submitted to US academic dermatology lab in 1997: • 444 (64.5%) positive by histologic examination (PAS); • 35% diagnosed as onychodystrophy; • Cost of treating all 688 (medication plus blood work): $590/patient = $405,920 total; • Cost of testing before treatment ($50/patient) = $296,360 total. **Conclusions:** *"We conclude that it is more cost effective to first confirm the diagnosis of onychomycosis and then treat only those with infection."*
Bootman (1998)*	Economic evaluation: • Efficacy data from two recent trials; • Wholesale drug acquisition costs; • 1995 medical management costs by expert panel of dermatologists; • decision-analytic model; • Itraconazole: 200mg once daily for 12 weeks; • Terbinafine: 250mg daily for 12 weeks	Two terbinafine Vs itraconazole trials	**Total costs:** • Terbinafine: $697.55-699.11; • Itraconazole: $1216.49-1218.80. **Expected cost per disease-free day:** • Itraconazole: $2.05 and 2.37; • Terbinafine: $1.27; 1.50; • Terbinafine cost-effectiveness ratio = 1; itraconazole = 1.26 and 1.58; • Perspective not specified. **Conclusion:** *"Terbinafine is more cost-effective than itraconazole in the treatment of toenail onyhomycosis."*
Van Doorslaer (1996)	To conduct an economic evaluation of the most commonly used treatments in Germany for toenail onychomycosis from a health care payer perspective.	• Onychomycosis diagnosed on basis of both clinical and mycologic evaluation; • Infecting pathogen identified (at least dermatophyte Vs. non-dermatophyte);	**17 studies included in meta-analysis:** • At end of FU (12 months after starting therapy) there were substantial overlaps in efficacy rates of 3 oral therapies and mycologic cure rates in the same range: itraconazole (1 week pulse), 77.1%; itraconazole (continuous), 73.5%; terbinafine, 80.2%; • Clinical cure rates at end of FU: itraconazole (1-week pulse), 72.5%; terbinafine,

Citation	Objective	Included studies	Results/Conclusions
		• Dose of drug (itraconazole, terbinfine, or ciclopirox varnish) reported clearly; • Duration of therapy at least 12 weeks; • Site of infection (finger- Vs. toe-nails) clearly identified) along with number of patients for each infection site; • Only the primary antifungal administered during study; • Minimum 6-month FU; • Excluded: trials with suboptimal dosing schedules; trials with >1 drug used for treatment or oral + topical.	72.5%; itraconazole (continuous), 49.3%. **Cost-effectiveness analysis:** • Itraconazole (1-week pulse) had most favorable average cost-effectiveness ratio: DM1107/success and the highest number of successful responses of comparators; • Next most efficient therapy: terbinafine, DM 1224/success; • 1-week pulse itraconazole and terbinafine had similar cost-effectiveness ratios and wide confidence intervals around efficacy rates. **Sensitivity analysis:** relative ranks of drugs changed when efficacies were modified within ranges, so analysis results were not conclusively in favor of either drug. **Conclusions:** *"Itraconazole is an effective, broad-spectrum triazole used as continuous or pulse therapy in the treatment of onychomycosis. Itraconazole (1-week pulse) and terbinafine are the most cost-effective therapies for toenail onychomycosis."*
Arikian (1994)	To conduct a pharmaco-economic analysis, combining clinical efficacy with economic costs of oral drugs available in Austria, Belgium, Canada, Finland, France, Germany, Greece, Italy, the Netherlands, Portugal, Spain, Switzerland, and the UK, to determine the most cost-effective treatment of onychomycosis of the fingernail and toenail.	Meta-analysis was used for efficacy estimates for drug interventions (success, relapse, and adverse effect rates) for: • Griseofulvin (GRI); • Itraconazole (ITR); • Ketoconazole (KET); • Terbinafine (TER) but meta-analytic methods incompletely reported: no search strategy or selection/exclusion criteria; Expert opinion of dermatology panel to specify processes for treatment and for adverse effects management	**Meta-analysis** (weighted point-estimate): • Fingernail: TER had highest success rate (95.0%) of comparators; • KET (80.9%); ITR (71.1%); GRI (59.6%); consistent with expert opinion. • Toenail: Overall clinical success rates were considerably lower than for fingernails, but same ranking and consistency with expert opinion: TER (78.3%); ITR (68.7%); KET (40.8%); GRI (17.5%); **Costs** ("current values" for drug acquisition, administration, laboratory tests, physician fees)**:** TER was the most effective therapy in relation to cost (therefore with the lowest cost-effectiveness ratio) for both finger- and toe-nail infections in all of the health care systems analyzed. **Conclusions:** *"This cost-effectiveness analysis demonstrated that TER may be considered the best choice for therapy of both fingernail and toenail onychomycosis. From an initial, perfunctory standpoint, a erroneous conclusion could be drawn in favor of GRI, due to substantially lower acquisition cost. However, our analysis has shown otherwise."*
Einarson (1994)	To conduct an economic analysis of oral antifungal drugs (griseofulvin, ketoconazole, terbinafine) currently registered and used in treating onychomycosis of fingernails and toenails with meta-analysis of	• All published clinical trials; • Expert panel of 5 Canadian dermatologists to determine management.	**Toenails:** • Terbinafine success: 78.3%; • Ketonazole success: 40.8%; • Griseofulvin success: 17.5%. **Costs** (100% government payer perspective)**:**

Citation	Objective	Included studies	Results/Conclusions
	published studies for rates of success, relapse, and side effects		• Terbinafine: $1049.77; • Griseofulvin: $1388.54; • Ketonazole: 1936.48. **Cost-effectiveness ratios** (compared to terbinafine)**:** • Griseofulvin: 2.49; • Ketonazole: 2.48. **Disease–free days:** • Terbinafine: 1073; • Ketonazole: 798; • Griseofulvin: 569. **Conclusions:** *"The drug which had the lowest expected cost, and cost per disease-free day, was terbinafine; it was also shown to be the most cost-effective for both fingernails and toenails, with a shorter treatment time, better success rate, the greatest amount of disease-free days, and better financial outcome than other study comparators."*

Table 4: Additional questions with responding literature (including applicable systematic reviews)

Notes: **Lighter-shaded rows indicate studies conducted with pharmaceutical company funding or declaration of interest by an author.**
*** indicates review indexed or titled as systematic but which on close inspection does not fully qualify**

Reference	Study type/details	Results/comments
Diagnosis: • **Diagnostic test performance** • **Prediction models/risk factors** • **Biopsy/sampling methods**		
Shenoy (2008)	Cross-sectional: • diagnostic yield of KOH, culture, histopathology with PAS against standard of at least one positive result by any of these methods: • Nail scrapings or clippings from patients with clinically suspected onychomycosis	101 patients with clinically suspected onychomycosis under consideration for treatment: • 84 had positive result by at least one of the study tests and were considered true positive samples; • KOH: Se, 54%; • Culture: Se, 42%; • PAS: Se, 90%; significantly higher than other tests. **Conclusions:** *"histopathologic diagnosis with PAS staining was the most sensitive among the tests. It was easy to perform, rapid, and gave significantly higher rates of detection of onychomycosis compared o the standard tests, namely KOH mount and mycological culture."*
D'Hue (2008)	Cross sectional: diagnostic yield of GMS and PAS on nail biopsies from academic dermatopathology files: • 20 cases with PAS confirmed onychomycosis; • 51 PAS negative cases of possible onychomycosis. • All cases also stained with GMS	**GMS Vs PAS:** • All 20 PAS positive cases also positive for fungi with GMS; • 5/51 PAS negative cases positive with GMS; • GMS detected significantly more cases of onychomycosis than PAS (35% v. 28%, p<0.0253); • GMS stains were qualitatively superior, detecting more hyphae more quickly with lower power objectives than PAS. **Conclusions:** *"GMS stains detected 5 additional cases of onychomycosis in 51 PAS-negative cases…The GMS stain was also qualitatively superior, as it allowed easier detection of the fungal hyphae on low and intermediate power microscopic examination. In contradiction, detection of fungal hyphae by PAS stains frequently required more time-consuming examination oft he specimen on high magnification before detecting the fungal hyphae. In our practice we now preferentially use the GMS stain for the diagnosis of onychomycosis and suggest that the GMS stain may represent the new gold standard for the diagnosis of onychomycosis."*
Gupta (2008)	Cross-sectional: diagnostic yield of PCR assay for *Trichophyton rubrum* DNA ; calcofluor white fluorescence microscopy; and culture: • 83 patients with "previously confirmed diagnosis of *T rubrum* onychomycosis and who were receiving antifungal therapy; • No disease-free controls; • Timing and method of original diagnosis not	83 samples: • Calcofluor white positive, 31.3%; PCR, 25.3%; combined, 46.9%; • Culture positive, 2.4%. **Conclusions:** *"These results suggest that the use of a direct DNA protocol is an alternative method for detecting Trichohyton infections. When this protocol is used, the presence of T rubrum DNA is directly detected. However, the viability of the dermatophyte is not addressed, and further methods need to be developed for the detection of viable T rubrum directly from nail samples."*

Reference	Study type/details	Results/comments
	reported; • Timing of sampling within course of antifungal tabulated but not accounted for in analyses; • Nail samples divided into 3 portions for PCR, fluorescence; and culture.	
Savin (2007)	Diagnostic accuracy: • Onochodiag kit (PCR-ELISA: Bioadvance, France) Vs direct microscopy and culture; • 3 university dermatology labs in France; • 438 patients with suspected onychomycosis not receiving antifungals; • 108 healthy controls; • 4 studies conducted in parallel: different labs, sampling personnel, and sampling sites; but no summary analysis of all results into standardized measures of test accuracy; i.e., 4 studies reported in one publication rather than the multi-center study of its title. • Positive and negative results defined by OD, including a "gray zone".	**Onychodiag kit:** • Accuracy Vs culture: Se = 83.6% (87.9% including "gray zone"); 75%-100% according to laboratory and sampling conditions • Sp against true negative healthy controls, 100%; • Positive in 68 samples that were sterile or cultured non-dermatophytes and where poor culture performance was attributed to inadequate sampling or contamination. • Distal samples: positive in 92% of proven dermatophyte onychomycosis. **Conclusions:** *"Finally, with either proximal or distal samples, Onychodiag provided a diagnosis of dermatophytic onychomycosis within 24 to 48 hours after sampling, and its sensitivity was close to that of mycological techniques applied to proximal samples."*
Chang (2007)	Diagnostic accuracy study: Can diagnosis be made from subungual hyperkeratosis alone? • 87 nail plate plus subungual hyperkeratosis specimens during study period; • US academic dermatology dept, 8 months in 2002.	66 cases diagnosed histologically: • 97% had hyphae in subungual component, 3% in nail plate only; • Modified approach required sufficient amount of subungual component in specimen; • 21 specimens diagnosed as dystrophic nail (both components negative for hyphae); • Insufficient information reported for calculation of sensitivity or specificity. **Conclusions:** *"The diagnosis of onychomycosis can be effectively made from histologic examination of subungual hyperkeratosis alone in most cases. This method circumvents the need to process nail plates in the vast majority of cases of onychomycosis (97%), resulting in a more efficient, less costly, and technically easier way of diagnosing onychomycosis. Submitting ample aunts of subungual hyperkeratosis is essential to increasing the diagnostic yield of nail clippings."*
Shemer (2007)	Comparison of sampling techniques: • subungual curettage Vs drilling; • nail samples from both methods divided into two parts for direct KOH examination and culture on Sabouraud's agar	194 patients with distal and lateral subungual onychomycosis: • For both techniques: culture sensitivity improved as location of sample became more proximal (drilling proximal Vs distal, $\chi^2 = 5.15$, P = 0.023;curretage proximal Vs distal, $\chi^2 = 4.2$, P = 0.041); • In each sample location, drilling had better culture sensitivity: drilling Vs curettage proximal, $\chi^2 = 11.9$, P =0.001; drilling Vs curretage proximal, $\chi^2 = 213.7$, P < 0.0001; • *Trichophyton rubrum* was the most common organism detected by both techniques in all sampling sites. **Conclusions:** *"The drilling technique was found to be statistically better than curettage at each site of sampling. With each technique, we found that the culture sensitivity improved as the location of the sample was more proximal. More types of pathogens were detected in samples taken by both methods from*

Reference	Study type/details	Results/comments
		proximal parts of the affected nails."
Walling (2007)	Cross-sectional: prediction model development	311 patients: • Toenail clippings submitted for pathology (PAS + histology), Jan 1999-Dec 2004; • 6 cases of non-dermatophyte infection excluded; • Demographic and clinical information from medical records used in chi square analysis; • 150 specimens (48.2%) were positive for dermatophytes; • Onychomycosis was significantly more likely to be diagnosed in men (78/130 specimens; 60%), versus women (72/181 specimens, 39.8%; p<.001); • Onychomycosis was significantly more likely to be diagnosed in patients > 64 yrs (27/41 specimens, 65.9%; p<.02); • Presence of tinea pedis was positively correlated with onychomycosis (p<.001); • Clinical distribution of nail dystrophy: involvement of third or fifth toenails of either foot (with or without dystrophy of other nails)correlated significantly with presence of dermatophytes (p<.025); • Dystrophy of great toenail: 82.6% of cases and positive for dermatophytes in 49.8% of those; but when both great toenails were dystrophic dermatophytes were less likely; • Dystrophy of first and fifth nails on the same foot, regardless of findings on the other predicted onychomycosis (p<.01) • Female gender was the only negative predictor. **Conclusions:** *Dystrophy of the third or fifth toenails, of the first and fifth nails on the same foot, unilateral dystrophy, male gender, age over 64, and the presence of tinea pedis are all independent predictors of onychomycosis. Presence of these patterns if dystrophy may help to clinically distinguish onychomycosis and guide laboratory testing."*
Szepietowski (2006)	Cross sectional/survey: prevalence of other dermato-mycoses in patients with toenail onychomycosis • Poland, 2004-05; • 241 dermatologists completed questionnaire; • Clinical diagnosis of onychomycosis confirmed by microscopy and culture.	2761 patients: • 1181 (42.8%) had concomitant fungal skin infections; tinea pedis the most common, 944(33.8%); • Other fungal infections: fingernail onychomycosis (7.4%); tinea cruris (4.2%); tinea corporis (2.1%); tinea magnuum (1.6%); tinea capitis (0.5%); • Presence of concomitant fungal infections depended on: number of involved toenails, duration of toenail infection, sex, age, education level, area of residence, type of fungus isolated from toenails. **Conclusions:** *The coexistence of toenail onychomycosis with other types of fungal skin infections is a frequent phenomenon. It could be hypothesized that infected toenails may be a site from which the fungal infections could spread to other body areas. Effective therapy for onychomycosis might therefore be essential not only to treat the lesional toenails but also to prevent spreading the infection to other sites of the skin."*
Lilly (2006)	Cross sectional: cost-effectiveness of diagnostic tests • KOH interpreted by dermatologist vs laboratory technician; • KOH-DMSO;	204 patients, mean age 69.5; 95.5% male: • PAS had highest Se = 98.8%; KOH-CBE,, Se = 94.3%; • DTM was least sensitive: Se = 57.3%; • KOH-CBE was significantly most cost-effective; PAS was least cost-effective; • Specificities not evaluated.

Reference	Study type/details	Results/comments
	• KOH-CBE; • Medicare and non-Medicare costs • Inclusion criteria: at least one toenail ≥25% involvement (subungual debris, onycholysis and/or onychauxis); • Exclusion: other nail dystrophies; ≥ 2 months of oral antifungal treatment within past year; topical ciclopirox within 6 weeks.	**Conclusions:** *"KOH-CBE should be the test of choice for practitioners confident in interpreting KOH preparations because of its combination of high sensitivity and cost-effectiveness."*
Fletcher (2004)	Cross-sectional: prediction model development	209 patients with nail disease: • Examining clinician completed 25-item questionnaire (history and clinical features questions) and obtained full-thickness nail clippings with subungual debris; • KOH, calcofluor white, and culture on modified Sabouraud agar (with and without cycloheximide); skin samples from body or foot as indicated; • Academic departments of dermatology and public health, UK. **Results:** • 32% of nails had positive culture and microscopy; 42% negative on all tests; 20% microscopy positive but culture negative; • 92% of isolates were dermatophytes; • Number of abnormal nails (excluding fifth toe): mean per patient, 5.1; median, 3; range, 1-18); • Features significantly related to positive mycology: tinea pedis in past year; scaling on one or both soles; white crumbly patches on nail plate; abnormal colored nail plate. **Conclusions:** *"Our results have shown one historical feature and three clinical features to be strongly associated with onychomycosis. The questionnaire has been revised to include only those stems and is being tested further with the aim of achieving a binary definition."*
Fletcher (2003)	Observational/agreement: • Between and within different groups for clinical signs and diagnosis of onychomycosis; • 9 observers: dermatologists; mycologists; GP; dermatology assistant; • Questionnaire from Fletcher (2004; above) tested on 9 patients with dystrophic nails (5 onychomycosis, 4 non-fungal nail disease); • Observers also asked to suggest underlying diagnosis.	• Substantial inter-observer agreement for only 3 clinical signs: abnormal nails on both hands; abnormal toenails; abnormal fingernails. • More specific signs of nail disease (e.g. onycholysis) elicited weaker agreement. • All observers showed accuracy in making clinical diagnosis of fungal nail disease: mean PPV, 0.91; 0.77 for non-fungal nail disease. **Conclusions:** *"Our results showed that agreement between observers, in recording signs of nail disease, was generally poor. The clinical diagnosis of onychomycosis was highly likely to be correct, suggesting that other criteria are being employed by individuals in reaching the diagnosis."*
Rich (2003)	Cross-sectional diagnostic yield: • in-office DTM vs. gold standard central	184 diabetic patients: • 61% male, 57% 55-64 yrs; 8% with fingernail onychomycosis and 33% clinical tinea pedis;

Reference	Study type/details	Results/comments
	laboratory culture in diabetic patients with suspected onychomycosis; • subset of diabetic patients from larger national survey; • Blinding of test interpreters not specified but inferred from office test Vs central lab. • No subjects without suspicion of disease.	• DTM and lab culture in agreement (+ve and –ve) for 62%; • DTM positive in 55%, culture in 43%; • Dermatophytes on culture in 91% of positives; • K = 0.25 (CI, 0.18-0.39); i.e., fair agreement beyond that expected by chance; • Where tests did not agree, lab culture negative twice as often as DTM (47 Vs 23 patients); **Conclusions:** *"DTM is a convenient and inexpensive culture test that can be used to confirm dermatophyte infections in diabetic patients with presumed onychomycosis. We found this test to be well suited for used in the primary care setting. Because oral antifungal agents are effective against dermatophyte species, which cause the vast majority of nail infections, diagnosis of onychomycosis requires confirmation of dermatophyte infection only, not identification of genus and species. DTM fulfills this requirement and has a diagnostic yield comparable to central laboratory culture."*

Weinberg (2003)	Cross-sectional:
	• Diagnostic accuracy of alternate tests (KOH, Bx/PAS, PAS) Vs gold standard Calcofluor white;
	• Samples from free edge of nail plate inpatients with suspected onychomycosis;
	• US urban hospital dermatology departments
		105 patients:
		• 93 (88%) had positive results on at least one of four tests;
		  ○ **Se:** KOH, 80%; Bx/PAS, 92%; culture, 59%; (P<.03);
		  ○ **Sp:** KOH, 72%; Bx/PAS, 72%; culture, 82%;
		  ○ **PPV:** KOH, 88%; Bx/PAS, 89.7%; culture, 90%;
		  ○ **NPV:** KOH 58%; Bx/PAS, 77%; culture, 43%.
		
		Conclusions: *"Bx/PAS is the most sensitive method for the diagnosis of onychomycosis. It is also superior to other methods in negative predictive value. It is indicated if other methods are negative and clinical suspicion is high, and potentially is the single method of choice for the evaluation of onychomycosis*

*Roberts (2003)	"evidence-based" guideline although methods not fully reported	**Distal and lateral subungual onychomycosis:** DLSO accounts for the majority of cases and is almost always due to dermatophyte infection. **Superficial white onychomycosis:** SWO is nearly always due to a dermatophyte infection, most commonly *T.mentagrophytes.* **Proximal subungual onychomycosis:** PSO without evidence of paronychia is an uncommon variety of dermatophyte infection often related to intercurrent disease (immunosuppression or HIV+). **Total dystrophic onychomycosis:** Any of the above varieties of onychomycoses may eventually progress to total nail dystrophy, where the nail plate is almost completely destroyed. **Conclusions:** • *"Treatment should not be commenced before mycological confirmation of infection.* • *Dermatophytes are by far the commonest causal organisms.* • *Culture of yeasts and nondermatophyte moulds should be interpreted carefully in each individual case. In the majority, yeasts are likely to be a secondary infection and nondermatophyte moulds to be saprophytic in previously damaged nails.* • *Topical treatment is inferior to systemic therapy in all but a small number of cases of very distal infection*

Reference	Study type/details	Results/comments
		or in SWO. • *Terbinafine is superior to itraconazole both in vitro and in vivo for dermatophyte onychomycosis, and should be considered for first-line treatment, with itraconazole as the next best alternative.* • *Cure rates of 80-90% for fingernail infection and 70-80% for toenail infection can be expected. In cases of treatment failure the reasons for such failure should be carefully considered. In such cases either an alternative drug or nail removal in combination with a further course of therapy to cover the period of regrowth should be considered."*
Reisberger (2003)	Cross-sectional: culture and KOH Vs histopathology with PAS to determine which yields highest rate of positive results in patients with suspected onychomycosis: • Clippings processed with KOH, 2 cultures, and PAS; • Gold standard unclear	Material from 387 nails of 350 patients with suspected onychomycosis: • Culture: 100 cases positive; • KOH: 156 cases positive; • PAS: 182 positive; • Total number positive by at least one method: 438. PAS gave the highest rate of successful recognition of mycotic infection. **Conclusions:** *"The histopathological evaluation of PAS-stained nail clippings is very quick and easy to perform, and will increase the frequency of diagnosing onychomycotic disease above that achieved by culture and KOH preparation alone. However, because information concerning the vitality of the fungi and accurate identification of the specific pathogen is not available through this investigation alone, mycotic culture continues to remain the indisputable "gold standard;' of mycological diagnosis."*
Gianni (2001)	Cross-sectional: Patients with finger- and toe-nail alterations suggestive of onychomycosis (Urban academic hospitals; northern Italy) evaluated with: • Direct microscopic examination of 40% KOH preparation; • Culture; • Histology with PAS, toluidine blue, and Gomori-Grescott.	172 patients: • In 60 patients, all tests were negative; re-examination confirmed nail changes due to conditions mimicking onychomycosis (eczematous dermatitis, traumatic alterations, psoriasis, lichen planus); • 59.3% positive on KOH; • Culture positive, 52.9%; • Histology positive, 54.6%; in 4 cases the only positive test result; • Printed results not interpretable within standard 4x4 table for test accuracy measures. **Conclusions: "***Histological examination of nail clipping specimens is a relatively inexpensive, rapid and easily performed procedure. It is useful to confirm or refute the results of routine microscopy and culture tests. Moreover, nail histopathological examination may help in ascribing a pathogenic role of non-dermatophyte isolates and evaluating the effectiveness of anti-fungal treatment."*
Lawry (2000)	Cross-sectional: diagnostic accuracy with: • blinded test readers; • diagnostic standard: clinical morphologic findings suggestive of onychomycosis plus at least one positive test result.	63 adults with nail changes highly suggestive of onychomycosis in one of 3 categories (FTO, DLSO, or SWO) contributed nail samples from distal free edge of nail plate. All samples received each of 6 tests: culture on Sabouraud agar with chloramphenicol and cycloheximide (Mycosel agar); culture on Littman-oxgall agar; routine histopathological examination with PAS; KONCPA; kONCFLU; KONCBLE. **Results:** • PATHPAS: Se= 85%; • KONCPA: Se = 57%; • KONCFLU: Se = 53%;

Reference	Study type/details	Results/comments
		• KONCBLE: Se = 53% • Culture on Mycosel agar: Se = 32%; Littman –oxgall, 23%; • The most sensitive combination of tests (both culture plus PATHPAS): 94%, not statistically different from PATHPAS alone. **Conclusions:** *"When onycomychosis is suspected clinically, PATHPAS is the single most sensitive of the diagnostic tests we evaluated. Because it is quickly performed and relatively operator independent, PATHPAS is practical for clinical and research purposes. Further study is needed to determine If sensitivity may be enhanced by combining PATHPAS with cultures obtained by several collection methods (clipping, curettage, and shaving). Such combinations may serve as sensitive and efficient strategies for diagnosing onychomycosis."*
Harvey (2000)	Cross-sectional: Comparison of sampling sites for culture: • Nail plate; • Nail bed; • Subungual debris; • Patients with clinical evidence of onychomycosis; • Clinical appearance as gold standard	30 patients: • 83% had positive culture, 76% of these dermatophytes; • Specimens from subungual debris produced more positive cultures than nail plate or nail bed (P<.01): dermatophytes, non-dermatophyte molds, and yeasts. **Conclusions:** *"Cultures from the subungual debris were more likely to be positive for dermatophytes, nondermatophytic molds, and yeasts than were cultures from the deeper nail bed or nail plate."*
Mehregan (1999)*	Economic evaluation: testing Vs empiric treatment **Case series:** • **cost study only;** • **outcomes not considered.**	688 dystrophic nail samples from the same number of patients submitted to US academic dermatology lab in 1997: • 444 (64.5%) positive by histologic examination (PAS); • 35% diagnosed as onychodystrophy; • Cost of treating all 688 (medication plus blood work): $590/patient = $405,920 total; • Cost of testing before treatment ($50/patient) = $296,360 total. **Conclusions:** *"We conclude that it is more cost effective to first confirm the diagnosis of onychomycosis and then treat only those with infection."*
Heikkilä (1996)	Isolation of fungi by drilling Vs clipping: • Specimens for direct microscopy and fungal culture taken from the same nail by both methods; • Microscopy with KOH; • Culture on 3 different media (brain heart infusion agar, selective agar for pathogenic fungi, Sabouraud maltose agar).	101 nails with clinically suspected onychomycosis: • Direct microscopy: no differences between methods (45/101 and 48/101 positive); • Culture: clipping, 23/45 positive; drilling, 20/48 positive; • Yeast and molds found equally frequently with the two methods and in microscopy- positive and negative groups; • *Trichophyton rubrum* was the most common dermatophyte; • By combining results of both techniques, it was possible to detect five additional positives compared with clipping alone and two compared with drilling alone. **Conclusions: "***By combining results of clipping and drilling techniques, it can be seen that 31/101 specimens (31%) were positive for dermatophyte culture compared with 27/101(27%) with clipping alone and with 20/101 (20%) with drilling alone. Out of a total of 101 nail specimens taken with both methods, 24/84 toenails and 10/17 fingernails were both direct microscopy and culture negative. The present study shows no differences in the number of positive specimens on direct microscopy obtained by the clipping and drilling*

Reference	Study type/details	Results/comments
		techniques. Regarding the culture of dermatophytes, clipping appeared to be slightly better than drilling. These results contradict previous results in which drilling was found to be superior to clipping. Combining these two techniques gives the best culture results but is unpracticable in routine work."
Liu (1993)	Cross-sectional: KONCPAS Vs: • KOH; • Histopathology; • culture • patients with clinically suspected onychomyosis, mixed toe- and fingernails; • Group A:18 participants with severe infection from a topical antifungal study; • Grouio B: 74 from private practice; • full-thickness samples taken as proximally as possible without patient discomfort	
Suarez (1991)	Cross-sectional: PAS-stained histology Vs culture in patients with suspected onychomycosis	2 groups: • A: 17 dermatophyte culture positive; 18 PAS positive; • B: 14/74 culture positive; • B according to specimen length: $\geq$ 3mm, 52 specimens; < 3,mm, 22 specimens (printed results not interpretable by standard 4x4 table). **Conclusions:** *"Routine histopathologic analysis of the nail plate alone is a useful complementary method to fungal culture for diagnosing onychomycosis."*

Summary: diagnostic <u>testing for onychomycosis:</u> Searches without date or language restrictions did not identify credible diagnostic accuracy studies for commonly used tests, all of which are reported to have substantial shortcomings. Those studies that are available suffer from:

- lack of a consistently used single gold standard;
- lack of test interpreter blinding;
- biased selection of cases and controls with inclusion of subjects currently receiving oral antifungals or with test-negative rather than disease-free controls;
- inconsistent use of numbers of nails versus patients as the unit of analysis;
- circular reasoning in which the objective of research is to identify the test yielding the highest percentage of positive results for cases of clinically suspected infection, thus effectively using clinical suspicion as the gold standard and seeking diagnostic yield rather than test accuracy;
- inadequate reporting of data from which to calculate standard test performance indicators (Se, Sp, PPV, or NPV).

All factors above preclude valid comparisons among tests. Several studies report that histopathology with PAS or GMS staining may be useful additions to routine KOH or culture in onychomycosis. However, these studies also suffer from the shortcomings listed above.

Molecular or genetic marker tests for dermatophytes are under development but have yet to reach routine clinical use, definitive proof of superiority to alternate methods, or demonstration of impact on treatment processes or outcomes. Diagnostic testing for onychomycosis would benefit from a dedicated systematic review effort.

Reference	Study type/details	Results/comments
2. Treatment: • **topical and systemic agents;** • **surgery;** • **combinations;** • **long term outcome: control Vs. cure.**		
Topical agents		
Crawford (1999; 2007)	Cochrane systematic reviews of RCTs: To assess effects of topical treatments in successfully treating (rate of failure) fungal infections of the toenails and in preventing recurrence	**Placebo comparisons:** • Ciclopiroxolamine Vs placebo: RR, 0.32; CI, 0.20-0.52 at 48 weeks; • Fungoid tincture Vs placebo: RR, 0.17; CI, 0.02-1.14 at 12 months; **Treatment Vs treatment:** • 2% butenafine Vs 5% tea tree oil: RR, 0.03; CI, 0.00-0.47 at 36 weeks; • 1% clotrimazole Vs tea tree oil: clotrimazole better but NS; • Two 5% amorolfine lacquer formulations with different vehicles used twice weekly for 4 weeks both achieved RR of 1.00; CI, 0.85-1.18 at 3 and 14 days after end of treatment. **Conclusions***: Evidence for the management of topical treatments for infections of the toenails is sparce. There is some evidence that ciclopiroxolamine and butenafine are both effective but they both need to be applied daily for prolonged periods (at least one year). The six trials of nail infections provided evidence that topical ciclopirololamine has poor cure rates and that amorolofine might be substantially more effective but more research is required."*
Casciano (2003)	See systemic agent section below	126 trials in 121 papers. 2 trials for nails:
Gupta (2002)	Pharmacoeconomic analysis: • MEDLINE/EMBASE: • Articles in English; • 1966-2000; • Excluded: reviews; • Treatment algorithm developed; • Meta-analysis to calculate average mycologic and clinical response rates for various agents (ciclopirox nail lacquer 8%; pulse and continuous itraconazole, griseofulvin, fluconazole, terbinafine).	Costs per patient, per mycologic cure, and per disease free day tabulated in the article. **Conclusions:** ***"…****ciclopirox 8% nail lacquer, which has recently become available in the larger size of 6.6mL, is a cost-effective agent for the management of toenail onychomycosis."* .
Hart (1999)	Print publication of Cochrane review [Crawford (1999; 2007), above]: • Efficacy and cost-effectiveness of topical treatment for skin and nails of feet; • RCTs with no language restrictions; • topical treatment;	• Two 5% amorolfine lacquer formulations in different vehicles both achieved cure rates close to 90% after 6 weeks (smaller trial); • Clotrimazole solution and tea tree oil both achieved cure rates close to 10% after 6 months. **Conclusions:** *"Neither trial of nail infections showed significant differences between alternative treatments."* See Crawford (1999;2007), above.

Reference	Study type/details	Results/comments
	• Skin infection trials needed culture and microscopy to establish presence of dermatophytes; • Nail infection trials needed culture to establish presence of dermatophytes; • Excluded: trial covering sites other than foot where data specific to foot could not be extracted; • Outcomes: cure confirmed by culture and microscopy for skin, culture for nails	
Summary: topical agents Some topical agents may be effective (see Table 2). However, trials are small, few in number, and do not directly compare topical to systemic agents.		
Systemic agents		
Crawford (1999; 2007)	Systematic review of RTCs; duplicates Hart (1999), below	• 2 included trials for nails • One small trial: amorolfine 5% nail lacquer formulations in two different vehicles: both achieved cure rates of 94% after 6 weeks; • In another trial: clotrimazole solution (cure rate of 18% after 6 months) performed better than tea tree oil (11%), although not significantly. **Conclusions:** *"Evidence about the efficacy of topical treatments for nail infections is very sparce. Little can be concluded about the role of these agents in curing infected toenails. Rigorous research is overdue, perhaps starting with a placebo controlled trial of amorolfine 5% nail lacquer***."**
Bell-Syer (2004)	To assess the effects of all oral treatments for toenail onychomycosis	Cochrane review protocol
Gupta (2004)	A cumulative meta-analysis to determine: • Whether the cure rate for systemic antifungal agents has remained consistent over time; • Mycological and clinical response rates in open Vs randomized studies; • Studies evaluating efficacy of oral antifungal agents (terbinafine; pulse or continuous itraconazole; fluconazole; griseofulvin); • Standard accepted dosage regimens, treatment duration, and FU; • Medline 1966-2002	36 studies included: • RTCs: change in efficacy, first trial to overall cumulative meta-average: terbinafine, 78%±6% to 76 ± 3% (P = 0.68); itraconazole pulse, 75 ±10% (P =0.25); itraconazle continuous,63 ±5% (P = 0.47); fluconazole, 53 ±6% (P = 0.41); griseofulvin, 55± 8% P = 0.41); • RCTs Vs open studies, mycological cure rates: terbinafine, 76 ±3% Vs.83 ± 2% (P = 0.0028); itraconazole pulse, 63±7% Vs. 84± 9% (P = 0.0001); fluconazole, 48 ± 5% Vs. 79 ± 3% (P = 0.0001). **Conclusions:** *"The cumulative meta-analysis of cure rates for RCTs suggests that over time, as new RCTs have been conducted, the efficacy rates have remained consistent. The efficacy rates of open studies are substantially higher compared to RCTs and may therefore over estimate cure rates."*
Cribier (2004)	To review published studies of the safety and efficacy of terbinafine in special patient populations: • Diabetes mellitus; • HIV infection;	**Terbinafine in special populations** **Diabetes:** • 3 studies (total n = 217); designs not reported • Mycological cure rates at the end of FU: 64%-89%; • Cure rates in ITT analyses (2 studies from which review authors could calculate): 62%; 78%;

Reference	Study type/details	Results/comments
	• Receiving immunosuppressive therapy; Onychomycosis due to non-dermatophyte infection.	• ITT complete cure rate: 41%; • No significant side effects; • Tolerability "very good" in 91% of patients; • NS differences in mycological or clinical cure rates for diabetics Vs non-diabetics. **HIV:** • 2 studies (total n = 31); designs not reported; • Mycological cure in 30%. **Organ transplant recipients:** • 3 case series (total N = 45); • Cure rates, 86-100%; • Significant decrease in blood cyclosporin levels with terbinafine, but not reflected in clinical status. **Non- dermatophyte infection:** • 11 clinical trials or case series; • Total N = 389; • Wide range of pathogens and methods of recording outcome; • This review does not pool results. **Conclusions:** *This review suggests that terbinafine is a safe and effective treatment for onychomycosis in high risk populations. However, the majority of these studies only included small numbers of patients and larger clinical trials are needed, especially in patients with HIV infection."*
Krob (2003)	To compare the efficacy of terbinafine with that of itraconazole in the treatment of toenail onychomycosis caused by dermatophytes	• Medline; • 1966-1999; • English; • Randomized studies; • Patients received not less than 3 months or cycles and no more than 4 months or cycles of either terbinafine or itraconazole.
Casciano (2003)	Cost-effectiveness evaluation from managed care perspective	40 clinical trials with 3248 patients: • Terbinafine has the highest success rate for both fingernails (96.55%) and toenails (81.15%); • Terbinafine also had the lowest relapse rate: 6.42%; • Terbinfine dominated all comparators for cost-effectiveness (fingernails and toenails). **Conclusions:** *"Based on the patient-level analysis, we concluded that terbinafine is the most cost-effective therapy in the management of onychomycosis from a managed care perspective. Furthermore, at the policy level, increased utilization of terbinafine among onychomycosis patients is likely to reduce the managed care organizations' per member per month cost."*
Haugh (2002)	Systematic review of controlled trials	<u>terbinafine Vs. placebo:</u> • 3 trials: Terbinafine (424 patients); placebo (164); • FU to 12 weeks in one trial, 12 and 24 in one;

Reference	Study type/details	Results/comments
		• Advantage of terbinafine to achieve mycological cure was significant from 12 weeks of treatment (RR, 9.07; CI, 5.14-16.02). Terbinafine Vs. itraconazole: • 4 trials: Terbinafine (622 patients); itraconazole (642); • 2 trials had 12 weeks FU, 2 had 16 weeks; • Statistically significant advantage of terbinafine for negative culture and microscopy at the end of FU (RR, 1,64; CI, 1.48-1.81). Terbinafine Vs. griseofulvin: • 2 trials: Terbinafine (185 patients; griseofulvin (190). • One trial: 24 weeks of terbinafine; 48 weeks of griseofulvin; the other trial, 12 weeks for both; • Statistically significant higher rate of negative microscopy and culture at 24 weeks for terbinafine (RR, 1.31; CI, 1.10-1.56). **Conclusions:** *"A significant advantage in favor of terbinafine was observed."*
Crawford (2002)	Meta-analysis of RCTs	Pooled analysis of two trials comparing mycological cure rates: terbinafine (250mg/day for 12 weeks) Vs. continuous itraconazole (200mg/day for 12 weeks): • Statistically significant difference in favor of terbinafine for 11- and 12-month outcomes; • Risk difference, -0.23 (CI, -.32 to -0.15); • NNT, 5 (CI, 4-8); • Analysis of clinical cure rates was not possible due to variety of definitions used in effectiveness studies. **Conclusions:** *"There is good evidence that a continuous regimen of terbinafine (250mg/d) for 3 months is the most effective oral treatment for fungally infected toenails. Consensus among researchers evaluating oral antifungal drugs for onycomycosis is needed to establish meaningful definitions of clinical cure. Most trials were funded by the pharmaceutical industry; we found little independent research, and this may have introduced bias to the review."*
Gupta (2002)	Cost-effectiveness analysis	Costs per patient, per mycologic cure, and per disease free day tabulated in the article. **Conclusions:** ***"…****ciclopiox 8% nail lacquer, which has recently become available in the larger size of 6.6mL, is a cost-effective agent for the management of toenail onychomycosis."* .
Jansen (2001)	**Cost-effectiveness analysis using data from LION study: double-blind multicenter RCT** • Adults (18-75) with dermatophyte nychomycosis; • Excluded: use of drugs known or believed to interact with either study agent Costs (direct medical costs only) estimated from	**496 (or 506) patients randomized:** • T12 group, 126 patients; • T16 group, 123; • I3, 131 (CI, 41-107); • I4, 126. Mycological cure rates: T12, 76%; T16, 81%; I3, 38%; I4, 49%; Complete cure (mycological cure plus 100% toenail clearing) rates: T12, 45.8% (CI, 6.4-55.3); T16, 55.1%

Reference	Study type/details	Results/comments
	expert opinion to the study sample To compare costs and effectiveness of two treatment regimens for dermatophyte onychomycosis: • Continuous terbinafine; • Intermittent itraconazole. Randomization to 4 parallel groups: • Terbinafine 250mg/day for 12 or 16 weeks (groups T12 and T16); • Itraconazole 400 mg/day for 1 week in every 4 weeks for 12 or 16 weeks (groups I3 and I4); Perspective: health care system (Finland, Germany, Iceland, Italy, Netherlands, UK).	(CI, 45.0-65.0); I3, 23.4% (CI, 15.4-31.3); I4, 25.9% (CI, 17.70-34.0). Percentage of patients completely cured at week 72 in terbinafine groups (T12, T16) was significantly greater ($P \leq 0.0046$) than those initraconazole groups. **Conclusions:** *"From the perspective of the healthcare system, continuous terbinafine is less costly and more effective than intermittent itraconazole."*
Gupta (2000)	To determine the most cost-effective treatment for dermatophyte onychmycosis of the toes in the United States in 2000.	English language: • 1966-1999; • Discussion of efficacy of comparators (griseofulvin, terbinafine, pulse or continuous itraconazole, fluconazole, ciclopirox nail lacquer); • Clinical and mycologic diagnosis of onycomycosis with distinction dermatophye Vs. non-dermatophyte • Required duration of study: griseofulvin (>6 months); itraconazole (≥ 3 months); terbinafine (≥ 3 months); fluconazole (≥ 3 months; ciclopirox (≥ 6 months); • Required dosage: griseofulvin (500mg/day); itraconazole pulse (200mg bid for 1 week each month and successive pulses 1 month apart); itraconazole continuous (200 mg/day; terbinafine (250mg/day); fluconazole (q7d); ciclopirox applied once weekly to daily); • End-point of therapy clearly defined; • Site of infection clearly defined.
Gupta (1999)	To determine the most cost-effective treatment for dermatophyte onychomycosis of the toenails in the USA in 1998/1999. • English language studies using itraconazole, terbinafine, fluconazole, or griseofulvin to treat onychomycosis of the toenails; • 1966-1999; Preference for RCTs, but other studies were included.	Article tabulates efficacy and cost results but does not summarize in text. • The two most cost-effective agents for dermatophyte onycomycosis are pulse itraconazle and terbinafine, followed by fluconazole, continuous itraconazole, and griseofulvin; • Sensitivity analysis with minor changes in efficacy rates reverses the rank order of pulse itraconazole and terbinafine. **Conclusions:** *"The two most cost-effective regimens for the treatment of dermatophyte toenal onychomycosis are itraconazole (pulse) and terbinafine; the least cost0effective comparator is griseofulvin, despite the fact that it has the cheapest drug acquisition cost per tablet."*
Epstein (1998)	Systematic review: To analyze studies on oral	26 articles:

Reference	Study type/details	Results/comments
	treatment of toenail onycomycosis to aid clinical decisions; Medline; Selection: • Description of results in toenails; • Culture and microscopy plus clinical evaluation; • Excluded: single case reports; series< 15; results combining finger- and toenails; report of toe nails cured but not subjects cured.	• Standard course of terbinafine: DFN in 35-50% (CI, 38-55) of patients; itraconazole, 25-40% (CI, 25-45); • 45% of patients showed mycological failure during one year. **Conclusions:** *"Standard courses of terbinafine achieved a disease free nail in approximately 35% to 50% of patients. For itraconazole, the relevant disease-free nail rate was about 25% to 40%. Disease reappearance is an important issue; unfortunately data are lacking as to its frequency."*
Einarson (1994)	Economic analysis: • Canada; • Government payer perspective	**Toenails:** • Terbinafine success: 78.3%; • Ketonazole success: 40.8%; • Griseofulvin success: 17.5%. **Costs** (100% government payer perspective)**:** • Terbinafine: $1049.77; • Griseofulvin: $1388.54; • Ketonazole: 1936.48. **Cost-effectiveness ratios** (compared to terbinafine)**:** • Griseofulvin: 2.49; • Ketonazole: 2.48. **Disease–free days:** • Terbinafine: 1073; • Ketonazole: 798; • Griseofulvin: 569. **Conclusions:** *"The drug which had the lowest expected cost, and cost per disease-free day, was terbinafine; it was also shown to be the most cost-effective for both fingernails and toenails, with a shorter treatment time, better success rate, the greatest amount of disease-free days, and better financial outcome than other study comparators."*
Summary: Systemic agents With few exceptions, Terbinafine remained the most effective and cost-effective treatment during the publication period of 1994-2003. Pulse itraconazole had equivalent effectiveness and cost-effectiveness among oral agents, depending on perspective and currency. Too few studies directly compared topical and oral agents to generalize from results.		
Combinations		
Grover (2007)	See Surgery section below	
Jennings (2006)	IRON-CLAD TRIAL: • Terbinafine (250mg/day for 12 weeks) alone;	**504 patients randomized** (terbinafine alone, 255; + debridement, 249): • 74.4% had received previous therapy for onychomycosis and had at least 2 affected toenails;

Reference	Study type/details	Results/comments
	or • Terbinafine (250mg/day for 12 weeks) plus aggressive debridement (weeks 12-48); • Randomization methods and power calculations not reported • 33 US podiatric medical centers; • Standardized nail involvement/outcome assessment template: compete cure (mycologic cure + clinical clearing); clinical cure (≥ 87.5% clearing); clinical effectiveness (mycologic cure + plus at least 5mm of new clear growth); mycologic cure (negative KOH and culture); • Outcome assessment by non-investigators although treatment precluded full blinding.	• 80% had long-standing onychomycosis and most had ≥ 62.5% nail involvement at baseline • Patient histories equivalent in both arms: athlete's foot in past year, 55.2%; hyperhidrosis, 33%; ≥1 risk conditions (ingrown nail, trauma or athlete's foot, hyperhidrosis), 88.1%. **Efficacy:** • Complete cure, mycologic cure, clinical effectiveness increased incrementally for both arms during study; • Addition of debridement increased efficacy rates consistently across all assessments; • Cure rates at 48 weeks were higher for debridement group: complete cure, 37.8% Vs 32.5% (CI, -3.0-1.4%); mycologic cure, 67.5% Vs 62,6% (CI, -4.0-1.3%); clinical effectiveness, 55.3% Vs 52.3% (CI, -6.0-1.2%); clinical cure, 59.8% Vs51.4% (CI, -1.0-17.1%); statistical significance reached only for clinical cure at week 24 (P = .002); • At study end, more patients reached greater nail plate clearing in debridement group. **Safety:** • Low incidence (similar in both groups) of treatment-emergent adverse events; • Most frequent treatment-emergent adverse events: mild-to-moderate nausea, arthralgia, or headache; • Low adverse event rates: ingrown nail, headache. **Conclusions:** *"The addition of debridement to terbinafine treatment resulted in significantly more patients with a high percentage of clear nail, suggesting that aggressive debridement, used as an adjunct to terbinafine treatment, may provide a cosmetic advantage by reducing the visible signs of onychomycosis. Moreover, we found that in some subgroups, debridement added to terbinafine treatment seemed to increase efficacy compared with terbinafine alone (eg, subgroups with > 75% nail involvement and those with a > 10 year onychomycosis duration) (results not shown). In these subgroups, such outcomes may have a positive impact on patient discomfort and on patient perception of disease and thus may result in improvements in patient-reported outcomes. Further analysis of patient-reported outcome data from this study should help determine the extent to which clinical cure can contribute to patient-reported outcomes in onychomycosis."*
Gupta (2005)	RCT: 8% topical ciclopirox plus oral terbinafine • 8 North American dermatology clinical trial centers; • Patient entry criteria: positive KOH or culture diagnosis of infection, one great toenail > 60% involvement and/or lunula/matrix involvement; Exclusions: any condition potentially interfering with treatment or evaluation (severe tinea pedis, liver function abnormality, psoriasis, nail abnormalities); failure of previous therapy with terbinafine or itraconazole; systemic therapy within 12 weeks; topical therapy within 4 weeks. **3 treatment arms:** 1) 48 weeks ciclopirox + 8 weeks terbinafine	**Total N = 73:** • > 90% of patients took at least 80% of assigned treatment; • Mycological cure by group at 48 weeks: 1, 66.7%; 2, 70.4%; 3, 56.0%; differences NS; • Clinical success at 48 weeks by group: 1, 45.0%; 2, 37.5%; 3, 43.5%; differences NS; • Effective cure at 48 weeks: 1, 40.0%; 2, 33.3%; 3, 34.8%; NS; • Safety: adverse events evenly distributed among groups included GI disturbance, skin and subcutaneous tissue disorders, abnormal laboratory values. **Conclusions:** *"The combination regimen was well-tolerated and had high compliance. The data suggest that combination therapy may be an alternative regimen to continuous terbinafine in the treatment of moderate to severe dermatophyte toenail onychomycosis."*

Reference	Study type/details	Results/comments
	250mg/day (21 patients); 2) 48 weeks ciclopirox + 12 weeks terbinafine 250 mg/day (27 patients; 3) 12 weeks terbinafine 250mg/day (25 patients).	
Summary: combination treatment: Currently available research does not provide definitive answers regarding benefits of combinations over best single drug therapy.		
Surgery		
Grover (2007)	RCT: avulsion of single involved nail plus: • Ketonazole 2% cream without (group 1) or with (group2) occlusion; • Oxiconazole 1%cream without (group 3) or with (group 4) occlusion; • Topical therapies applied once daily; • Patients reviewed monthly and treatment continued until re-growth of completely normal nail; • Cured patients continued FU at least 6 months without further therapy. • Direct microscopic examination at each monthly visit ; • 10 patients per group.	40 patients randomized: • High drop out rates: group 1, 30%; group 2, 40%; group 3, 40%; group 4, 20%; • No sample size calculation or method of randomization reported; • Mycologic cure by group in patients completing therapy: 1, 43%; 2, 67%; 3, 33%; 4, 75%; • All cases of TDO (18% of total enrollment) failed to respond; • Of 27 patients completing therapy: 56% cured; • FU at 12-15 months: recurrence in 2 group 1 patients. **Conclusions:** *"Contrary to earlier reports, surgical nail avulsion with topical antifungal agents was not found to be a very encouraging modality for the treatment of onychomycosis. Both oxiconazole and ketoconazole delivered comparable results. Occlusion improved the treatment outcome, although the difference was not statistically significant. As a subtype, TDO showed poorest response. Surgical nail avulsion followed by topical antifungal therapy cannot be generally recommended for the treatment of onychomycosis."*
Summary: nail avulsion for treatment of onychomycosis Only one trial has compared nail avulsion to another treatment. Due to design weaknesses, its results are neither statistically significant nor reliably generalizable to other patients.		
`Long term outcome: • **How should chronic onychomycosis be managed?** • **Control Vs cure** • **Definitions of cure**		
Long term outcome		
Sigurgeirsson (2002)	5 year FU RCT in Iceland: continuous terbinafine Vs intermittent itraconazole (first intervention) with patients not achieving clinical cure (or relapse or re-infection) at 18 months receiving a second course of terbinafine	FU using Icelandic component of LION study: 151 patients randomized to terbinafine (74) or itraconazole (77): • 268 patients screened, 110 excluded for negative mycology, withdrawal of consent, protocol violations, failure to return for FU; • 143/151 completed the first 18 months of study, 144 followed up to 58 months; • 3 centers; • No significant differences in baseline characteristics (age, sex, infecting organism, weight, number of nails involved, or percent of involvement; • Median duration of FU, 54 months.

Reference	Study type/details	Results/comments
		Results: • Mycological cure without second intervention in 46% of terbinafine group Vs 13% of itraconazole group (P<.001); • Mycological (53% Vs 23% and clinical relapse (48% Vs 2%) rates significantly higher in itraconazole group; • 72 patients received second intervention with terbinafine: 88% mycological cure; 76% clinical cure. **Conclusions:** *"In the treatment of onychomycosis, continuous terbinafine provided superior long-term mycological and clinical efficacy and lower rates of mycological and clinical relapsed compared with intermittent itraconazole."*
Cribier (2001)	Qualitative systematic review: • Topical and systemic antifungals • Medline to June 2000; • Studies reporting outcomes > 1 year after initiation of treatment with: amorolfine; ciclopiroxolamine; fluconazole; griseofulvin; itraconazole; ketoconazole; and terbinafine; • End point 1(EP1): number of patients with negative mycology at FU/ total number in study; probably most equivalent to results in clinical practice; • End point 2 (EP2): patients with negative culture after FU/ number at week 48; proportion of patients cured sat one year who were still free of fungus at 18, months, at 2 years, or at 4 years; i.e., persistence of response in responders; • Clinical end point (EPclin): number of patients clinically cured (total recovery or >90% improvement).	17 studies reporting results> 48 weeks: only oral antifungal results reported. • Ketoconazole 200mg/day: EP-1, 11% at 18 months; EP-2, 43%; • Griseofulvin, 1g/day: EP-1, 43% at 18 months; EP-2. 72%; • Fluconazole once/week up to one year: EP-1, 49% at 18 months; EP-2, 91%; • Itraconazole 200mg/day or 400 mg/day 1 week each month for 3-4 months: EP-1, 37% at18 month, 53% at 2 yrs; EP -2, 76% at 4 years; • Terbinafine 250 mg/day for 12-16 weeks: EP-1, 62% at 18 months, 72% at 2 yrs, 60% at 4 yrs; EP-2, 80% at 18 months, 81% at 2 yrs, 71% at 4 yrs; • In the only study comparing long-term efficacy of terbinafine Vs itraconazole, EP-1 at 18 months was significantly higher (66% Vs 37%, p<0.001) with continuous terbinafine that intermittent itraconazole; • Clinical cure rates: 21% at 60 weeks and 37% at 72 weeks with fluconazole; 27% at 18 months, 35% at 2 yrs with itraconazole; 48% at 18 months, 69% at 2 yrs, 50% at 4 yrs with terbinafine; **Conclusions:"***…this critical review suggests that the long-term efficacy achieved with terbinafine is superior to that obtained with griseofulvin, ketoconazole, fluconazole, or itraconazole."*
De Cuyper (1999)	Narrative synthesis of two multi-center trials with long-term (2-year outcomes) for subjects from the authors' center.	**Study 1 (RCT):** • Terbinafine (250 mg/day) Vs terbinafine (500 mg/day). Both 16 weeks: • 16 weeks of treatment for both groups (total n = 125); • Week 48: MC in terbinafine 250mg group =89.6%; **Study 2 (RCT):** • Terbinafine (250 mg/day) Vs. itraconazole (200 mg/day for 12 weeks); • 372 subjects, 331 evaluable; assessed for clinical, direct microscopy, and culture outcomes at 4, 8, 12, 24, 36, 48 weeks; • 48 week assessment for categorical global clinical outcome: minimal residual lesions (minimal distal

Reference	Study type/details	Results/comments
		hyperakeratosis and/or onycholysis); moderate improvement; or failure); • Terbinafine at week 48: 75% of patients showed complete cure or MRL and negative culture; 5% showed MRL with positive culture but negative microscopy; 15% moderate improvement with negative culture; 5% failed therapy; • Terbinafine at 2 years: 80% MRL or clinical cure with negative culture; 15% moderate improvement with negative culture; 5% failed therapy; • Itraconazole at 48 weeks: 23.5% clinical cure of MRL and negative culture; 4% MRL but positive culture; 35% clinical failures. **Conclusions:** *"..the high rates of mycological and clinical cure achieved by terbinafine at 48 to 72 weeks are maintained 2 years or more after completion of the study. In this connection, terbinafine is superior to itraconazole, and is likely to provide significant benefits when used as part of any policy designed to eradicate onychomycosis in the community."*
Epstein (1998)	Systematic review: To analyze studies on oral treatment of toenail onycomycosis to aid clinical decisions; Medline; Selection: • Description of results in toenails; • Culture and microscopy plus clinical evaluation; • Excluded: single case reports; series< 15; results combining finger- and toenails; report of toe nails cured but not subjects cured.	26 articles: • Standard course of terbinafine: DFN in 35-50% (CI, 38-55) of patients; itraconazole, 25-40% (CI, 25-45); • 45% of patients showed mycological failure during one year. **Conclusions:** *"Standard courses of terbinafine achieved a disease free nail in approximately 35% to 50% of patients. For itraconazole, the relevant disease-free nail rate was about 25% to 40%. Disease reappearance is an important issue; unfortunately data are lacking as to its frequency."*
Tosti (1998)	Case series: • 47 patients who were mycologically cured 6 months after discontinuation of treatment (open RCT) with systemic antifungals; • 16 received terbinafine 250mg daily for 4 months; • 16 received 500 mg terbinafine daily, 1 week/month for 4 months; • 15 received itraconazole 400 mg daily ,1 week/month for 4 months; • 30 patients clinically and mycologically cured; • 17/30 patients mycologically cured with residual nail dystrophies (10 with traumatic dystrophies, 7 with "doubtful" (possible residual onychomycosis) nail abnormalities; • Al patients examined every 3 months for up to	36/47(76.5%) patients completed 3 years of FU: 12 who received continuous terbinafine 250 mg; 3 pulse terbinafine 500 mg; 11 pulse itraconazole 400 mg: • 9/36 (25%): onychomycosis originally associated with tinea pedis (approximately equal numbers in all groups); • 8/36 (22.2%) had relapse during FU: 2, terbinafine 250 mg; 2 terbinafine 500 mg; 4 itraconazole 400 mg (one of whom had residual dystrophy entering FU); • All other patients were clinically cured entering FU; • 7 relapses (all due to original organism and all associated with mild nail abnormalities): month 6 (terbinafine 500 mg); month 12 (itraconazole 40 mg); month 15 (terbinafine 250 mg); month 18 (terbinafine 250 mg and itraconazole 400 mg); month 36 (terbinafine 500 mg); **Conclusions:** *"This study shows that 22.2% of all patients with onychomycosis successfully treated with systemic antifungals experienced a relapse. The relapse rate increased from 8.3% at month 12 to 22.2% at month 36. Relapses were more common in patients treated with pulse itraconazole (4/11) than in patients treated with continuous (2/12) or intermittent (2/13) terbinafine. Statistical analysis did not reveal any significant difference between relapse rtes in the three groups."*

Reference	Study type/details	Results/comments
	3 years with clinical and direct microscopy evaluations and samples for culture taken from any abnormal-appearing nails; • Patients considered positive for relapse with positive microscopy or culture.	
Summary: long term outcome All available treatments provide less than perfect long term cure, although terbinafine has the lowest reinfection and relapse rates. No method to reliably distinguish between relapse or incomplete cure and reinfection after cure has been reported.		
4. How should chronically dystrophic nails be managed?		
Avner (2006)	Case series: • Patients with fifth toenail deformity with or without onychomycosis and with onychomycosis of other nails; • Treatment with 250mg terbinafine/day for 4 months; • Is failure of fifth toenail onychomycosis treatment a marker for other nails?	50 patients, of whom 43 completed study: 43% had callus lateral to fifth toe at baseline, suggesting mechanical pressure; 49% had fifth toenail onychomycosis: • After treatment: 19% of fifth toenails and 57% of other nails were clinically cured; • Entire group of 43: clinical cure rate for fifth nail, 9% Vs other nails, 47% (P<0.05); • Mycological cure rates: fifth nail, 52%; others, 58%; • Callus lateral to fifth toe was associated with poor clinical result (P< 0.01). **Conclusions:** *"Clinical improvement of the fifth toenail after systemic antifungal therapy is less favorable and does not correspond with the clinical cure of the other toenails, mostly because of mechanical factors. Therefore, patients should be told to adjust their expectations as to the visual results of their antifungal treatment."*
Cabral (2006)	Case series to determine prevalence of fungi in morphologically abnormal nails: • 990 consecutive unselected cases; • Clinical suspicion of fungal infection; • Finger- Vs toe-nails not specified; • Cytology and pathology laboratory in the Netherlands; • Some samples apparently from Brazil; • Non-formaldehyde fixative; • Microwave-enhanced processing; • Paraffin sections with PAS and hematoxylin counter-stain.	990 samples: • Diagnosis equivocal in < 1%; • Prevalence of invasive hyphal structures, 606/990 (61%); • RR for fungal infection in morphologically abnormal nails higher:< 20 years; diabetics >60 years. **Conclusions:** *"The 61% positivity rate for fungi found justifies direct submission of samples from abnormal nails for histological confirmation in order to avoid unwarranted treatment."*
Fletcher (2003)	Observational/agreement: • Between and within different groups for clinical signs and diagnosis of onychomycosis; • 9 observers: dermatologists; mycologists; GP; dermatology assistant;	• Substantial inter-observer agreement for only 3 clinical signs: abnormal nails on both hands; abnormal toenails; abnormal fingernails. • More specific signs of nail disease (e.g. onycholysis) elicited weaker agreement. • All observers showed accuracy in making clinical diagnosis of fungal nail disease: mean PPV, 0.91; 0.77 for non-fungal nail disease.

Reference	Study type/details	Results/comments
	• Questionnaire from Fletcher (2004; above) tested on 9 patients with dystrophic nails (5 onychomycosis, 4 non-fungal nail disease); • Observers also asked to suggest underlying diagnosis.	**Conclusions:** *"Our results showed that agreement between observers, in recording signs of nail disease, was generally poor. The clinical diagnosis of onychomycosis was highly likely to be correct, suggesting that other criteria are being employed by individuals in reaching the diagnosis."*
Summary: Management of dystrophic nails: The majority of dystrophic nails have fungal infections and the accuracy of clinical judgments for fungal Vs non-fungal etiologies of these nail is reasonable although imperfect. Virtually no research addresses management of non-fungally infected dystrophic nails.		
Control Vs. Cure		
Gupta (2003)	Systematic review: definitions of efficacy • Medline, 1966-2001; Cochrane skin group trials register; • Studies treating dermatophyte onychomycosis with oral agents; • Exclusions: non-dermatophyte infections; non-English language report; or special population.	44 studies included: • Mycologic cure was predominantly defined as negative microscopy and culture; • Clinical response or clinical cure were variably defined and indicated by a range of terms. **Conclusions:** *"Standard and explicit definitions are required for the accurate comparison of the effectiveness of various therapies."*
Summary: control Vs. cure There is no literature directly relevant to this question. Results of the single review cited here parallel the discussion of diagnostic tests above.		

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VA TECHNOLOGY ASSESSMENT PROGRAM

Mission Statement

To enhance the health of veterans and the nation by providing and fostering technology assessment for evidence-based health care

Values

Integrity and pride in the work that we do

Quality products that are clinically valid and methodologically transparent

Objectivity in evaluating and presenting research evidence

Commitment to continuous quality improvement and to the guiding principles of evidence based practices

Flexibility in responding to changes in VA and the larger healthcare environment

Innovation in designing products and their dissemination to best meet VA's needs

Accessibility of products and services